A STUDY ON AUDITORY AND VISUAL EVOKED POTENTIAL IN YOUNG HEALTHY FEMALES DURING DIFFERENT PHASES OF MENSTRUAL CYCLE.

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirements for

the award of the degree of

M.D PHYSIOLOGY

Branch V

APRIL 2016

CERTIFICATE

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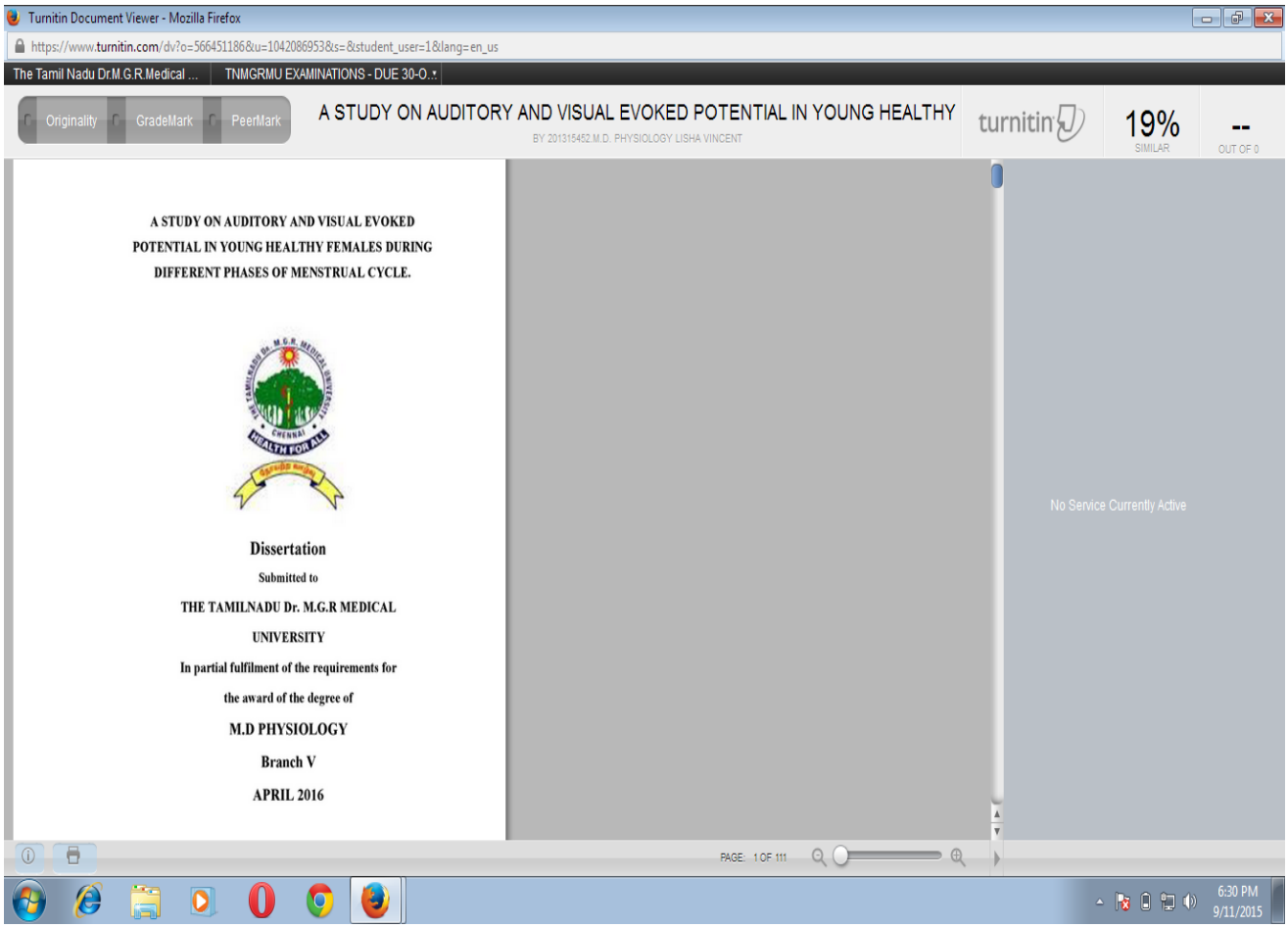
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ABSTRACT:

Introduction: Ovarian hormones have long been known to affect the sensory information processing in brain. Brainstem Auditory Evoked Potential (BAEP) and Visual Evoked Potential (VEP) are simple non-invasive electrophysiological tests for hearing and vision assessment. Studies have shown mixed results regarding variation in auditory & visual neural conduction during different phases of menstrual cycle.

Aims and Objectives: The present study is done to evaluate BAEP &VEP in normal healthy females during different phases of menstrual cycle.

Material and methods: This cross sectional study was conducted among 80 young healthy female 1st year nursing students of age group 18-20years having regular menstrual cycle. After taking a detailed menstrual history & clinical assessment of hearing and vision, BAEP & VEP was recorded in menstrual phase (Phase 1), proliferative phase (Phase 2) & secretory phase (Phase 3) of menstrual cycle using RMS Aleron 401 EMG/NCV/EP system.The data are analyzed by one way ANOVA Posthoc test followed by Dunnet t test.

Result: The absolute latencies of all the waves of the BAEP and VEP as well as the inter-peak latencies of BAEP waves showed a decrease in the proliferative phase with statistically significant decrease in wave V and inter-peak latencies III-V and I-V of BAEP waves and P100 latency of VEP wave. On the other hand, the absolute latencies of the various BAEP and VEP waves as well as the inter-peak latencies of BAEP waves in the secretory phase were increased with statistically significant increase in the same above wave latencies and inter-peak latencies of BAEP and VEP

waves. The VEP amplitude and BAEP amplitude ratio showed an increase in proliferative phase as compared to secretory phase.

Conclusion: The study showed that BAEP and VEP changes in the menstrual cycle phases are attributable to the ovarian hormones oestrogen and progesterone, which mainly modifies the central processing of auditory and visual neural conduction.

Key words: Menstrual cycle, Brainstem Auditory Evoked Potential, Visual Evoked Potential, Oestrogen, Progesterone.

1. INTRODUCTION

Menstrual cycle is the cyclical changes that occurring in the body of a female after attainment of puberty. This cycle starts with menarche, which is the beginning of her reproductive life and ends with menopause, where she completes her fertile period. It represents the periodic preparation of the reproductive system, so that the female can give birth to a baby.[1]

The external manifestation of this attainment of puberty in a female is the monthly discharge of blood through the vagina called menstruation. This is actually a monthly cycle, as the word menstrual comes from a Latin word mensis, that is a lunar month of 28 days.[2, 3] The average duration of menstrual cycle is 28 days starting from the first day of bleeding or the menstrual phase to the start of the next.[1,4] The menstrual flow usually last for 3 to 5 days and the average blood loss during each cycle is about 30 ml. [1]

The menstrual cycle is mainly divided into endometrial cycle, that mainly focus on endometrial changes during the cycle and ovarian cycle, that mainly concerned with ovarian changes during each cycle. Endometrial cycle consists of menstrual phase, proliferative phase and secretory phase. Ovarian cycle consists of follicular phase and luteal phase separated by ovulation in between the two.[5] The dominant event that occurs in menstrual cycle is the release of mature ovum from the ovary called ovulation.[6]The main hormone secreted in the proliferative phase or the follicular phase of menstrual cycle is oestrogen and the main hormone secreted in the secretory phase or the luteal phase is progesterone.[5]

Menstrual cycle reflects interplay between the ovary, the pituitary gland and the brain.[5] These cyclical changes mainly focus on the reproductive tract for the fertilization and implantation of the fertilised ovum but it also influence different sensory modalities like vision, hearing, taste, touch, olfaction etc. Changes in gonadal hormones, especially oestrogen and progesterone have been suggested by many researchers, as the reason for change in sensory perception throughout the cycle.[7]

Evoked potential responses (EPR's) are indicators of functional integrity of sensory and cognitive pathways which are useful non invasive tool for neurophysiological research.[8] Brainstem Auditory Evoked Potentials (BAEP), an objective test which helps to assess conduction of auditory impulses through the auditory pathway up to midbrain. It also helps to assess severity of hearing deficits and middle portion of brainstem function.[9] These are very small electrical voltage potentials which are originated from brain in response to sound stimulus and can be recorded from the scalp.[10] It consists of five or more distinct wave forms labelled with Roman numerals lto V. Analysis of BEAPs consists of measuring the absolute latency, absolute amplitude, and inter peak latency (IPL) I-V, I-III and III–V waves.[11] All these parameters will show changes during different phases of menstrual cycle.

Visual Evoked Potential (VEP) assess the conduction of visual signals from the optic nerve up to the visual cortex. VEP records the electrical potential difference from the scalp evoked by visual stimuli, such as alternating checker board pattern on a computer screen. It includes three waves namely P100, N70, N135.[9, 11] The wave P100 peak latency, its amplitude and duration are the most commonly used parameters for assessing VEP studies.[11] The hormonal changes in menstrual cycle reflects changes in

the above parameters.

Various studies have showed that ovarian hormones modulate the conduction of sensory information in the brain. Throughout the menstrual cycle auditory and visual thresholds get varied systematically. The thresholds for olfaction, taste, touch, two point discrimination and perception of light have also been found to vary in different phases of menstrual cycle.[7] Menstrual cycle influences several clinical and neurological illness which may worse during the premenstrual phase. EEG also shows variation throughout the menstrual cycle. How hormonal variation influencing the cerebral physiology is still in controversy.[12, 13]

HYPOTHESIS & JUSTIFICATION

2. HYPOTHESIS AND JUSTIFICATION

HYPOTHESIS:

Variations in the Oestrogen and Progesterone levels during different phases of menstrual cycle may affect the auditory and visual neural conduction.

SCIENTIFIC JUSTIFICATION OF THE STUDY:

It is a well-established fact that the varying levels of sex steroids in different phases of menstrual cycle affect the mood and cognition of a female. A study done on prepubertal and aged mice showed that throughout the central auditory system estrogen receptors are present and they suggest that by regulating the transcription of genes via their classical estrogen receptor pathway, estrogens directly affect the processing of hearing in humans. According to different studies oestrogen has neurotrophic and neuroprotective effects throughout the CNS. Therefore it is of importance to understand the physiological actions and underlying mechanisms of estrogens in hearing and vision in order to develop estrogen-based strategies to protect hearing and vision.[14]

Various studies showed visual and auditory threshold variation in different menstrual cycle phases. [7] The gonadal hormonal action on central nervous system, especially in auditory and visual sensory perception can be assessed by evoked potential studies. This study will give awareness to the physician regarding the changes in BAEP and VEP during different phases of menstrual cycle while considering the normal values in female subjects. BAEP and VEP also provide

important diagnostic information regarding the functional integrity of auditory and visual pathways. Hence the present study is done to find the Auditory and Visual Evoked Potentials in young healthy females during different phases of menstrual cycle.

AIMS & OBJECTIVES

3. AIM AND OBJECTIVES:

1. To evaluate Brainstem Auditory Evoked Potentials (BEAP) in normal healthy females during different phases of menstrual cycle.
2. To evaluate Visual Evoked Potentials (VEP) in normal healthy females during different phases of menstrual cycle.

REVIEW OF LITERATURE

4. REVIEW OF LITERATURE

4.1. Menstrual cycle:

4.1.1. Introduction:

The regular cyclical changes that occurs in the reproductive system of a human female constitute the menstrual cycle.[1] These cyclical changes occurs regularly for a period of about one month.[15] It is regarded as the periodic preparation of female reproductive system for pregnancy, starting from sperm & ovum transport, fertilization & implantation.[5] The most conspicuous feature is the shedding of uterine mucosa externally manifest as periodic vaginal bleeding (menstruation).[1] Menarche is the term used to denote the first menstrual cycle.12 to 14 years is the usual age of menarche.[15]

4.1.2 Duration of menstrual cycle:

The length of the cycle averages at about 28 days, from the beginning of one menstrual cycle to the beginning of the next.[1] The 1st day of vaginal bleeding is considered as the day 1 of menstrual cycle.[1, 2] The duration of each cycle is never fixed in all females and the duration of all cycles is not same in one female. The cause for this is the menstrual cycle is frequently influenced by environmental, nutritional, psychological and social factors.[15]

4.1.3 Historical review of menstrual cycle: [16, 17, 18]

- In 1971 Schally and Guillemin found out GnRH.
- In 1672 Regnier de Graaf accurately described corpus luteum for the first time.
- In 1977 Goodman and Hodgen found that in humans, the ovulation occurs alternately in both ovaries due to the action of progesterone on follicular dynamics.
- In 1978 Belchetz found that the differential release of FSH and LH is related to the GnRH pulse frequency.
- In 1980 Knobil found that an intricate neuroendocrine control system is responsible for the cyclical pattern of reproductive activity in females.
- In 1982 Fritz and Speroff found that for continued follicular growth an estrogenic environment is essential.
- In 1982 Goodman et al found that after the degeneration of corpus luteum of previous cycle, it takes about 5-7 days for the development of new follicle to become dominant follicle.
- In 1984 Ferin et al found that the major site of action of estradiol is pituitary and that of progesterone and testosterone is hypothalamus.
- In 1986 Handelsman and Swerdloff found that the hypothalamic and pituitary peptidases rapidly degrade GnRH.
- In 1986 Kesner et al. found that almost coincidental release of LH along with electrical potential changes in arcuate neurons in monkey, on measuring the electrical activities of these neurons.

- In 1989 Hayflick et al. found that the gene for pre-pro-GnRH is present on the short arm of chromosome 8.
- In 1992 Wetsel et al. found that the release of GnRH can be modified by inputs from central nervous system, as these neurons are localized within the hypothalamus adjacent to other neuronal system.
- In 1994 Rance et al. found that a group of 7000 neurons present in hypothalamus synthesize and secrete GnRH.
- 1996 Guo et al found that Bax protein, apoptotic effector enzymes like Caspase-2, Caspase-9, and Caspase-11are invoved in follicular atresia.
- In 1997 Motta et al. found that by about 6 weeks of gestation the primordial germ cells proliferate and migrate to the genital ridge and then it is known as oogonia.
- In 2000 Johnson and Everitt found that prior to ovulation the rising level of progesterone exert an inhibitory effect on estrogen positive feedback. This will result in attenuation of midcycle LH surge. They also found that just before ovulation the follicle will have a size of 20 mm.
- In 2000 McGee found that to maintain a viable oocyte high level of estradiol and low androgen/estrogen ratio is needed whereas an androgenic environment favours oocyte degeneration.
- In 2002 Richard et al found that PGE2 and PGF2α are required in regulating transcription genes like CAAT, an enhancer binding protein β which is essential for changes in follicle wall and contents during ovulation.

- In 2002 Davis and Rueda found that one of the factor regulating luteolysis is the infiltration of reactive oxygen species in corpus luteum.
- In 2003 Cone et al. found that in late follicular phase the elevated level of estradiolupto 500pg/ml for 36 hours enhance the release of gonadotropins from pituitary.
- In 2004 Boime et al. found that in peripheral circulation the half-lives of LH and FSH are 20 and 180 minutes respectively.
- In 2004 Strauss and Williams found that in the corpus luteum, the principal site for estrogen synthesis is the granulosa cells as they express aromatase and the theca luteal cells synthesize androgen precursors like 17α-hydroxyprogesterone as they express 17α-hydroxylase and 17-20 lyase.
- In 2005 Wojcik-GladyszandPolkowska found that at the time of ovulation neuropeptide Y will potentiate GnRH stimulated LH secretion and suggested that neuropeptide Y is involved in sensitizing the pituitary during LH surge.
- In 2009 Rozell and Okrainetz found that follistatin plays an important role in conversion of estradiol producing granulose cells of dominant follicle to progesterone producing luteal cells of corpus luteum.
- Marcello Marpighi coined the term corpus luteum from the words corpora (bodies) and lutea (yellow).

4.1.4 Phases of menstrual cycle:

Menstrual cycle actually involves cyclical changes in ovary & uterus. The follicular phase & the luteal phase separated by ovulation constitute the ovarian cycle. The menstrual, the proliferative and the secretory phase constitute the endometrial cycle.[19]

4.2 The Ovary:

4.2.1 Ovarian morphology:

The ovary of an adult female is oval in shape with a width of 1.5 to 3 cm, a length of 2 to 5 cm and a thickness of 0.5 to 1.5 cm. Ovary weighs between 5 and 10 grams during the reproductive years. It consists of outer cortical region made of follicles and germinal epithelium. Medullary region made of connective tissue, interstitial cells and myoid like contractile cells. Hilum contains nerves, lymphatics and blood vessels that enter the ovary.[6]

4.2.2 Embryology of the ovary:

Three major cellular sources from which ovary develop are primordial germ cells, coelomic epithelial cells and mesenchymal cells. From the endoderm of the yolk sac primordial germ cells develop and differentiate into the oogonia. From the coelomic epithelial cells granulose cells develop. From the gonadal ridge mesenchymal cells develop and it forms the ovarian stroma. During the sixth week of gestation the primordial germ cells migrate to the gonadal ridge, there they undergo successive mitotic divisions to form multiple oogonia.[6]

4.2.3 Ovarian Cycle:

The cyclical changes occurring in the ovary during each female sexual cycle constitute the ovarian cycle.[20]The ovarian changes in this cycle completely depends on the anterior pituitary hormones LH and FSH.[4]

4.2.3.1 Phases of ovarian cycle:

1. Follicular phase

2. Luteal phase

4.2.3.1. A. Follicular phase:

It is otherwise called preovulatory phase. This phase begins with menstruation and ends with ovulation.[15, 19] Average duration of this phase is 14 days in a 28 day cycle. Duration of this phase is the most variable part of menstrual cycle. This phase is considered as the proliferative phase of endometrial cycle.[5]The major event in this phase is the maturation of follicles a process called folliculogenesis.[15]The main hormone regulating this phase is estrogen.[20]

Folliculogenesis :

At birth the female child's ovary contains primordial follicle made of ovum surrounded by single layer of granulosa cells. The ovum is kept at its prophase stage of meiotic division till puberty with help of oocyte maturation-inhibiting factor secreted by the granulosa cells. At the onset of puberty pulsatile secretion of gonadotropin-releasing hormone (GnRH) from hypothalamus triggers the release of

gonadotropins, the LH and FSH secretion from anterior pituitary. This leads to the formation of primary follicle having additional granulose cell layers.[4]Then secondary follicle having primary oocyte surrounded by multiple layers of cuboidal granulosa cells and differentiated stromal cells called theca cells develop. These granulosa cells secrete follicular fluid rich in estrogen[4,6]and growth factors[6] into the centre of the follicle creating a fluid filled space called antrum.[4,5,6] FSH alone stimulate the growth of primary follicle up to the antral stage.[4,5] The follicle is now named as tertiary or antral follicle.[6] Rapid increase in follicular size due to the accumulation of antral fluid results in the development of vesicular or Graafian follicle.[6]

About 10-15 primordial follicles start maturing but one of the follicles grow rapidly to form dominant follicle by about 6th day of cycle and the others regress to form atretic follicles.[1] In humans ,usually only one follicle will be selected as the dominant follicle from either ovary. The reason for the selection of only one follicle to become dominant follicle is uncertain, it is thought to be due to the ability of the follicle to secrete estrogen inside it as estrogen is required for final maturation.[1] Follicular diameter increases to 20 to 33 mm.[5]

4.2.3.1. B.Ovulation:

The process by which oocyte is released from the matured Graafian follicle of ovary into the abdominal cavity.[5]

Mechanism of ovulation:

Near the end of late follicular phase estradiol secretion increase rapidly from the dominant follicle. This raised level of estradiol produce a positive feedback effect on hypothalamus as well as anterior pituitary results in LH surge. This gonadotropin surge occurs when there is increase in estradiol concentration of 200 pg/ml for 50 hours in the blood.[5] This will cause rapid swelling of Graafian follicle due to increased blood supply & diffusion of plasma into the follicular fluid., Stretching of follicular wall results in the formation of an avascular area (stigma) over the most convex point of the follicle, release of proteolytic enzymes (plasmin and collagenase) & dissolution of follicular wall results in rupture and release of secondary oocyte from the mature follicle.[20]

Indicators of ovulation: [15, 20]

1. Increase in basal body temperature (BBT): Daily recording of early morning oral temperature will shows about 0.5 º c increases in basal body temperature after ovulation due to the thermogenic action of progesterone.
2. Fleeting lower abdominal pain: During ovulation the rupture of dominant follicle results in some bleeding into abdominal cavity which cause peritoneal irritation leading to short lived lower abdominal pain called mittelschmerz.
3. Increase in vaginal discharge and spotting
4. Spinnbarkeit: cervical mucus will be thinnest and its elasticity will be maximum at the time of ovulation so the cervical mucus collect at this time can

be stretched to about 10 cm or more. This elastic nature of mucosa is named as spinnbarkeit.

5. Fern test: Before ovulation when the cervical mucus is spread on a slide it shows an arborizing fern like pattern.This pattern will not appear after ovulation.
6. Ultrasound scanning and laproscopic examination demonstrating ovum in the abdominal cavity confirms ovulation.
7. Demonstration of LH surge: LH peak occurs just before ovulation. So the day of ovulation can be detected by daily estimating the plasma LH level in the periovulatory period.
8. The day of ovulation can be retrospectively calculated by subtracting 14 days from the first day of preceding menstruation, as it is a constant phenomenon that menstruation will come after 14 days of ovulation.

4.2.3.1. C. Luteal phase:

It is otherwise called postovulatory phase. This phase begins after ovulation and ends with starting of next menstruation. Average duration of this phase is 14 days. Duration of this phase is the most constant part of menstrual cycle. This phase is considered as the secretory phase of endometrial cycle.[20]The major event in this phase is the formation of corpus luteum. The main hormone regulating this phase is progesterone.[5]

The follicle that ruptures during ovulation gets filled with blood & forms corpus hemorrhagicum. Then there occurs proliferation of remaining granulosa and theca cells. The blood clotted inside the follicle is replaced rapidly with yellowish,

lipid rich luteal cells and then the follicle is called corpus luteum. Then the luteal cells started secreting estrogen and progesterone. Vascular endothelial growth factor is essential for the development of corpus luteum.[1]

If pregnancy occurs corpus luteum persists and forms corpus luteum of pregnancy. If pregnancy does not occurs it begins to degenerate after 24th day of the cycle and is eventually replaced by whitish scar tissue called corpus albicans.[1, 20] Thus on the 26th day of cycle, the hormones secreted from corpus luteum such as estrogen, progesterone and inhibin A will decrease to a lower level and feedback inhibition to the pituitary is removed leading to a raise in FSH & LH later, resulting in initiation of next ovarian cycle.[20]

4.3 Endometrial cycle: [5]

The cyclical changes in the endometrium due to the cyclical production of estrogen and progesterone from the ovary constitute the endometrial cycle.[5]

4.3.1 Phases of endometrial cycle:

1. Menstrual phase (1st to 5th day)

2. Proliferative phase (6th to 14th day)

3. Secretory phase (15th to 28th day) [5]

4.3.1. A. Menstrual phase:

If fertilization does not occurs, corpus luteum degenerates and the hormonal support of endometrium weans off. Lysosomal membrane of endometrial cells

undergoes destabilization and proteolytic enzymes will be released due to the reduction of steroids. This causes lysis of endometrium. Prostaglandin F2 alpha production increases which leads to vasospasm and endometrial ischemia. Areas of focal necrosis develops, these coalesce result in sloughing of endometrium and menstrual bleeding.[8] Superficial 2/3rd of the endometrium is sloughed off and the thin basal layer of about 2 mm thickness will be left behind.[20]

Endometrial debris contains blood, sloughed off tissue, serous fluid, fibrinolysin and prostaglandins. Fibrinolysin causes liquefaction of the clotted blood inside the uterine cavity. [20] Usually the duration of the menstrual flow last for 3 to 5 days. The blood lost in each cycle on an average is about 30ml.The loss of blood is mainly arterial, only 25% is of venous origin.[1]

4.3.1. B. Proliferative phase:

The proliferation of endometrium is the major event in this phase. Under the influence of estrogen endometrial epithelialisation occurs.[5] Endometrial proliferation occurs and thickness increases to 8-10 mm just before ovulation.[21] Endometrial glands lengthen and drawn out. Endometrial vascularity increased with the formation of more number of spiral arteries .Myometrial excitability increases in this phase.[15]

4.3.1. C. Secretory phase:

Under the influence of progesterone the uterine glands coiled and tortuous forming corkscrew shaped and vascularity of endometrium increases. [5] Spiral arteries become tortuous.Glandular cells store glycogen and starts secreting mucus and fluid in large quantities. These secretions contain glycogen, glycoproteins and glycolipids,

which sustain and facilitate attachment of conceptus.Due to the effect of progesterone the rapid proliferation of endometrium slows down, mitotic activity reduced and the endometrial thickness decreases to 5mm.[21] Endometrial veins form venous lakes and anastomosis. Myometrial excitability decreases in this phase.[15]

Transforming growth factor beta 3, Betacellulin and neuregulin-1 alpha and beta plays an important role in secretory phase endometrial maturation.[22]

4.4 Cyclical changes in the cervix: [15, 20]

- In proliferative phase- Increase in volume, elasticity and alkalinity of cervical mucus due to the influence of estrogen.
- In secretory phase- Decrease in volume, elasticity and increase in thickness of cervical mucus due to the influence of prgesterone.

4.5 Cyclical changes in the vagina: [15, 20]

- In proliferative phase- Vaginal epithelial cornification occurs due to the influence of estrogen.
- In secretory phase- Vaginal epithelial proliferation and thick mucus secretion occurs due to the influence of progesterone.

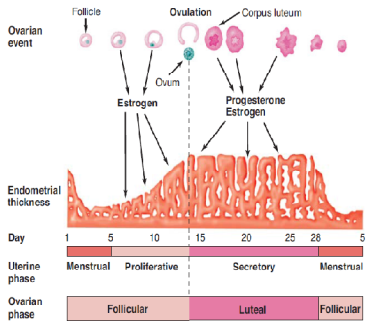


Figure1. Ovarian and uterine changes during the menstrual cycle.[1]

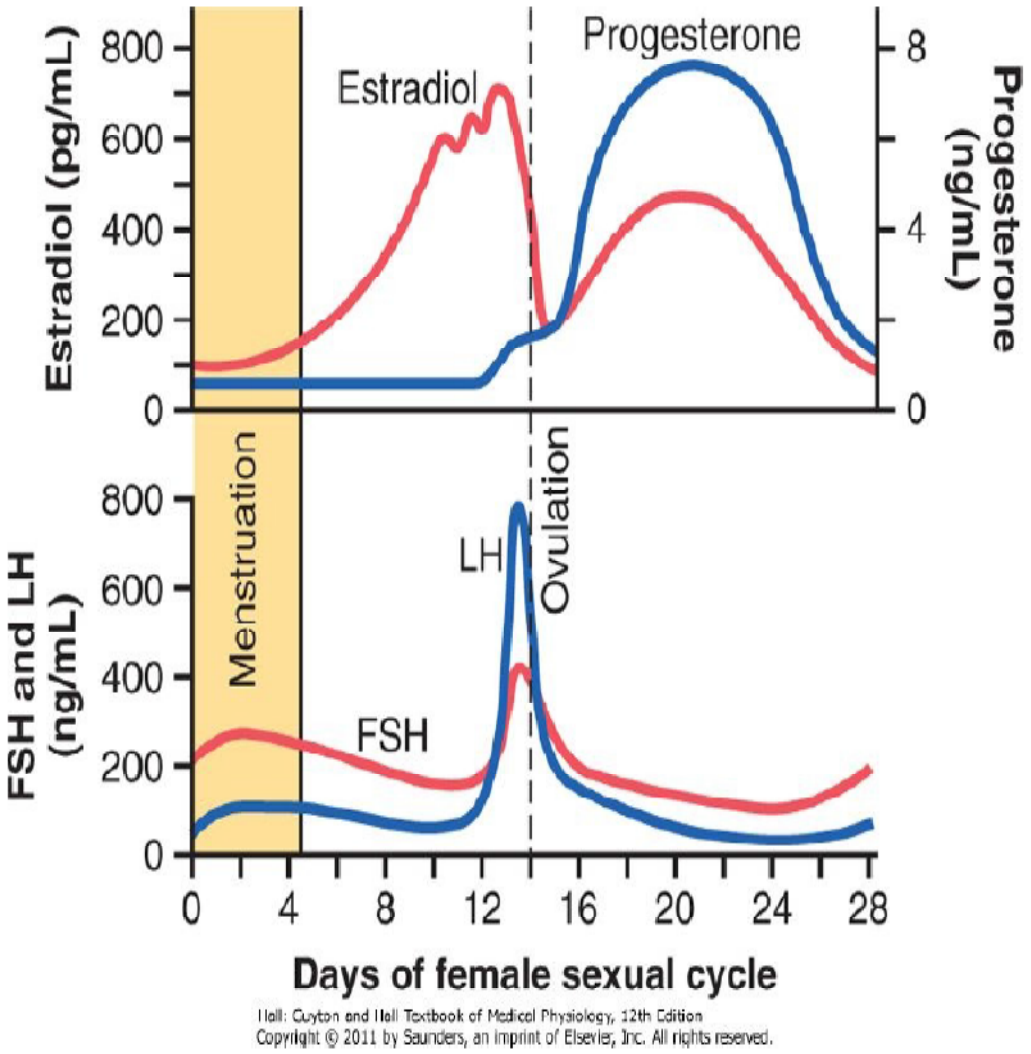


Figure 2: Approximate plasma concentration of gonadotropins and ovarian hormones during the menstrual cycle [4]

4.6 Hormones regulating menstrual cycle:

The cyclical changes in menstrual cycle is regulated by the hypothalamo-hypophyseal-ovarian axis.[5]

4.6.1 Role of hypothalamus:

Arcuate nucleus and preoptic area of hypothalamus secrete gonadotropin releasing hormone (GnRH) in a pulsatile manner into the anterior pituitary through hypohalamo-hypophseal portal system.[20]This will stimulate the gonadotrophs of anterior pituitary gland to release the gonadotropins namely FSH and LH.[5] The GnRH release is influenced by estrogen, progesterone, ratio of FSH and LH, dopamine, endorphins, dark and light cycles operating through melatonin. [20]

4.6.2 Role of anterior pituitary:

In response to GnRH stimulation the anterior pituitary secrete Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH).[20]

4.6.2. A. Follicle Stimulating Hormone

In the early part of follicular phase FSH secretion increases and then slowly declines. Along with the rise in LH there will be a rise in FSH secretion towards ovulation.[15]

4.6.2. B. Luteinizing Hormone

LH secretion started increasing about a day before ovulation and reaches peak concentration at about 8-10 hours prior to ovulation.[15]

4.7 Role of ovary:

Ovary secrete gonadal hormones namely estrogen and progesterone in response to gonadotropin secretion from anterior pituitary. It also secrete inhibin and activin.[5]

4.7. A. Estrogen :

They are C18 steroids secreted by the ovarian follicular granulosa cells, placenta, corpus luteum[1]and a minor quantity from adrenal cortex and testis.[20]17β-estradiol, estrone and estriol are the naturally occurring estrogens.Aromatase (CYP19) enzyme which converts testosterone to estradiol and androstenedione to estrone is very important for its biosynthesis**.** The latter reaction also occurs in brain, fat, liver and muscle.[1]

Its concentration starts increasing in the beginning of follicular phase, along with the growth of ovarian follicle. Then it rapidly raise from 8th day of the cycle and a peak concentration attained at about 48 hours before ovulation. This raise in estrogen cause LH surge by positive feedback mechanism resulting in ovulation. This is the major estrogen peak. A minor peak occurs 2 days after ovulation.[15]

Steps of synthesis of estrogen:

In the follicular phase, cholesterol to androstenedioneconvertion in the theca cell is primed by LH. But it cannot convert androstenedione to estradiol as the theca cells lack the enzyme aromatase. Androstenedione diffuses to the FSH stimulated granulose cells where aromatase convert it into estradiol.[5]

Metabolism:

In the blood, two percent of estradiol occurs in free form, 60% bound to albumin and 38% to the gonadal steroid-binding globulin (GBG) .Estradiol, estrone,

and estriol are converted to glucuronide and sulfate conjugates in the liver and excreted in the urine.[1]

Mode of action:

Estrogen binds with its nuclear estrogenreceptors ERα and ERβ encoded by genes on chromosome 6 and 14 respectively. ERα receptor is present mainly in uterus, heart, liver and kidneys. ERβ reseptor is present mainly in ovaries, lungs,hemopoietic system , prostate, gastrointestinal tract, and central nervous system (CNS).[1]This hormone receptor complex interacts with steroid-response elements on DNA results in new mRNA and protein synthesis.[23]Studies also demonstrate the non-nuclear ERs (membrane-associated ERs) can couple to second messenger system and generate rapid actions in the nervous system.[24]

Physiological actions:

1. Actions on female reproductive organs[15,20]

- On ovary: Estrogen stimulates ovarian follicular growth as well as ovarian growth.
- On fallopian tube: Estrogen increases fallopian tube motility by stimulating its smooth muscle contraction.
- On uterus: It causes uterine endometrial proliferation during the follicular phase of mensrual cycle.
- Along with progesterone it causes increase in uterine fluid secretion during the luteal phase of mensrual cycle.

- It increases the uterine size and blood supply, uterine myometrial excitability and uterine sensitivity to oxytocin.
- On cervical mucus secretion: It makes the cervical mucus clear, profuse and watery. These changes are more prominent at the time of ovulation.[15]
- On vagina: It converts cuboidal vaginal epithelium to cornified squamous epithelium.
- On external genitalia: It causes increase in size of clitoris, labia majora and minora.[20]

2. Actions on breast[15]

- It causes stromal tissue development in breast as well as increase in size of breast by deposition of fat.
- It causes growth of ducts in breast as well as pigmentation of areola.

3. Actions on development of secondary sexual characteristics[15]

Estrogen causes development of female pattern of body configuration such as broad hips and narrow shoulders, wide carrying angle, high pitched voice, female escutcheon of pubic hair, less body hair and more scalp hair, growth of internal gentalia both in size and function.

4. Actions on other endocrine organs[15]

It inhibits LH secretion by negative feedback effect and stimulates LH secretion before ovulation by positive feedback effect on anterior pituitary. It inhibits FSH and prolactin secretion. It stimulates adrenal androgen secretion. It increases

angiotensinogen synthesis from liver and activates rennin-angiotensin system. It increases thyroxine –binding globulin synthesis.

5. Actions on CNS[15,24]

It cause a selective enhancement of the growth and differentiation of axons as well as dendrites in the developing brain, modulating neurotransmitter production and release, enzyme activity, membrane potential, dendritic arborization, and synaptogenesis .

It affects the basal forebrain by regulating the cholinergic neurons that project to cerebral cortex and hippocampus, in where they play an important role in cognitive function.

It enhances cerebral blood flow through various mechanisms, such as vasodilation mediated by production of nitric oxide synthaseregulation of coagulation and thrombolysis and reduction of blood total cholesterol and low-density lipoprotein. [24]

It stimulates libido by activating limbic system and produces sexual behaviours by acting on suprachiasmatic area of hypothalamus. [15]

6. Actions on musculoskeletal system[15]

It inhibits osteoporosis and stimulates bone growth and determines the height of a female by causing epiphyseal closure.

7. Actions on electrolytes and water balance[15]

It helps in increased absorption of water and salt by kidney tubules.

8. Actions on lipid metabolism[15]

It lowers blood cholesterol level.

9. Actions on sebaceous gland and skin[1]

It makes the sebaceous secretion more fluid there by prevent acne and comedone formation and makes the skin soft in texture.

10. Action on blood vessel[20]

It produces rapid vasodilation by local release of nitric oxide, prostaglandins E_2 and prostacyclin and produce antivasoconstrictor effect through inhibition of endothelin-1release.

11. Nongenomic actions of estrogen[1]

Its effects on neuronal discharge in the brain and, possibly, feedback effects on gonadotropin secretion are mediated by cell membrane receptors that appear to be structurally related to the nuclear receptors. These effects are produced by stimulating intracellular mitogen-activated protein kinase pathways.

4.7. B.Progesterone

Progesterone is a C21 steroid secreted mainly by the corpus luteum, the placenta, and in minor quantities from the follicle, testes and adrenal cortex.[1]It is called non-hormone as it has no actions of its own.[2] Following ovulation its concentration starts increasing and reaches a peak at about 4 to 5 days after ovulation.

Towards the end of luteal phase, along with the regression of corpus luteum progesterone concentration declines to a lower level.[15]

Metabolism: [1]

It is metabolized to pregnanediol in liver and excreted as glucuronide conjugate in urine.

Mode of action: [1]

The stimulating effect of LH on progesterone secretion by the corpus luteum is due to activation of adenylyl cyclase and involves a subsequent step that is dependent on protein synthesis.

Physiological actions:

It acts on estrogen primed target organs. [2]The uterus, the breasts, and the brain are the principal target organs of progesterone.[1]

1. On uterus[1, 2, 4]

- It cause secretory changes in the estrogen primed endometrium.
- It decreases the intensity and frequency of uterine contractions.
- On the myometrial cells it has antiestrogenic effect. So it decrease myometrial excitability, their spontaneous electrical activity and sensitivity to oxytocin It also increases the myometrial membrane potential.
- It decreases the number of endometrial estrogen receptors and cause increase rate of conversion of 17β-estradiol to less active estrogens.

2. On breast[1]

It causes differentiation of estrogen primed ductal tissue.It also stimulates the development of lobules and alveoli and during lactation it supports the secretory function of the breast.

3. Onhypothalamo pituitary axis[15]

In large doses it prevents ovulation by inhibiting LH secretion and potentiate the inhibitory effect of estrogen.

4. On body heat production[1, 2]

Progesterone is thermogenicand also its metabolites etiocholanolone and pregnanediol.This may be the reason for the increase in basal body temperature at the time of ovulation.

5.On respiration[1]

It stimulates respiration. In the luteal phase the alveolar PCO_2 of females will be lower than that in males.

6.On electrolyte balance[1]

Large doses of progesterone produce natriuresis by inhibiting the action of aldosterone on kidney.

4.8. EVOKED POTENTIALS

4.8.1. Introduction:

In1987 Chiappa et al., defined evoked potential as the record of the electrical activity produced by groups of neurons within the spinal cord, brain stem, thalamus or cerebral hemispheres following stimulation of one or another specific system by means of visual, auditory, or somatosensory input.[25] The source of these activities is probably the summation of the action potentials generated by the afferent tracts and the electrical fields or activities of the synaptic discharges or post-synaptic potentials on those tracts.[26] Evoked potentials provide a measure of the function of sensory systems.[27]

4.8.2. Historical Reviews [9,25,26,28]

- DuBois Raymond - detected the changes in potentials as the impulse passed down the nerve trunk.
- Richard Carton – conceived the idea that as the nerve impulse flows in and out of brain its passage might be detectable. He discovered electroencephalogram and the cerebral potential changes evoked by sensory stimulation especially with visual stimuli.
- PravadichNeminsky – gave the first photograph of evoked potential recorded from cortex of a dog following stimulation of sciatic nerve. He also demonstrated that EEG could be recorded from an intact skull.
- Dawson -employed the neuro-electric responses to sensory stimuli that can be readily and non-invasively recorded using averaging techniques (1947).

- Adolf Beck – discovered the desynchronization of ongoing oscillatory activity on sensory stimulation, which is now recognized as alpha blocking of EEG. He found the positioning of electrodes which gave a response to light and a faint response to sound.
- Larionov – done mapping the topographic centers of temporal cortex of a cat in response to tuning fork stimuli of different pitches in 1889.
- Hans Berger named the spontaneous ongoing activity of the brain as "Das Elektrenkephalogram' and in 1940 launched EEG as a clinical neurologic test.

4.8.3. Clinical Utility Of Evoked Potentials (Eps) :[26]

The clinical utility of evoked potentials (EPs) is based on their ability to:

- Demonstrate abnormal sensory system conduction, when the history and/or neurological examination is equivocal
- Reveal subclinical involvement of a sensory system (''silent'' lesions), particularly when demyelination is suggested by symptoms and/or signs in another area of the central nervous system
- Help define the anatomic distribution and give some insight into pathophysiology of a disease process
- Monitor changes in a patient's neurological status.

EPs proved to be helpful in: [28]

a. Testing sensory functions when clinical examination is not reliable.

b. Investigating purely subjective symptoms and detect whether they have an organic origin.
c. Better assessing the causative mechanisms of neurological deficits and functional recovery.
d. Monitoring cerebral functions when the patient's condition is critical or at risk in the operating theatre or during intensive care.

4.9. Brainstem Auditory Evoked Potentials (BAEPs) / Brainstem Evoked Responses (BSERs) / Auditory Evoked Potentials (AEPs) [29]

Auditory Evoked Potentials are first recognised in human electroencephalogram in 1939.[30]The brainstem auditory evoked potential (BAEP)is an objective electrophysiological method for assessing the auditory pathways from the auditory nerve to the brainstem.[31]These are potentials recorded from ear and vertex in response to a brief auditory stimulation.[9] These potentials are produced with in the first 10 milliseconds of sound stimulus.[11,32] Therefore it is considered as short latency potential.[29,31] ABR is an early auditory evoked potential (AEP) and is not affected by sedatives and general anaesthetics therefore this test is a useful tool for assessing non-cooperative populations such as infants, young children and severe mentally retarded patients.[33] AEPs are now widely used in audiology, neurology, neonatology and anaesthesiology.[34]

It helps to assess: [9]

- Conduction through the auditory pathway up to the midbrain.
- Middle portion of midbrain function.
- Severity of hearing deficits in infants.
- Hearing in very young children and uncooperative patients.

4.9.1. Anatomical and physiological basis of BAEPs: [9]

The sound waves are transmitted from the external and middle ear to the inner ear. The inner ear consists of coiled cochlea containing organ of corti with the auditory receptors. The low frequency sounds affect the apical end of cochlea and high frequency sounds affect the basal end of cochlea. The amplitude of movement is directly related to the intensity of the acoustic signals. The stimulation of cochlea results in eighth nerve activity. The latency of eighth nerve discharge will be shorter from the basal compared to the apical end of cochlea. The eighth nerve is a bipolar neuron which is situated in the spiral ganglia, their dendrites go to hair cells and axons to the cochlear nucleus. The cochlear nucleus has three subnuclei namely, anterior ventral (AVCN), posterior ventral (PVCN) and dorsal cochlear nucleus (DCN) .The output of AVCN is through the ventral acoustic striae forming the bulk of trapezoid body to terminate in the superior olivary nuclei and inferior colliculus. The neurons in AVCN discharge at short latency to acoustic stimuli. The output of PVCN mostly goes through ventral and middle acoustic striae to terminate in superior olivary nuclei and inferior colliculus. Dorsal cochlear nucleus terminates in the superior olivary nucleus and contralateral inferior nucleus through dorsal striae. These neurons

discharge at long latency to acoustic stimuli. The excitatory input from both ipsilateral and contralateral AVCN reaches the medial superior olivary nucleus. The lateral superior olivary nucleus receives excitatory input from ipsilateral AVCN and PVCN and inhibitory inputs from contralateral AVCN and PVCN via trapezoid body. From the olivary nuclei, the impulses travel to ipsilateral and contralateral lateral lemnisci and to the inferior colliculi. The olivary nuclei are the first site in the auditory pathways where the neurons are affected in a nonlinear manner to binaural stimulation.The impulse from inferior colliculi reach medial geniculate body and then to auditory cortex, that is superior temporal gyrus and upper bank of sylvian fissure including the frontal and parietal opercula.

The orderly orientation of the neurons in dorsal cochlear, medial superior olivary, and lateral superior olivary nuclei results in summation of synaptic potentials to result in high amplitude electrical fields. The nuclei are connected by large myelinated fibre tracts and their synchronous discharge also generates cohesive voltage fields.

4.9.2. Brainstem electrical activity and its correlation with BAEP [9, 31]

After 10ms of acoustic stimulation, a series of potentials generated corresponding to the sequential activation of peripheral, pontomedullary, pontine, and midbrain portion of auditory pathways. The acoustic nerve and brainstem auditory potentials are volume conduction to surface recording electrodes**.** At the vertex and earlobe**,** these form vertex positive and vertex negative waves, which are known as BAEPs. It consists of five to eight[9] distinct vertex positive waveforms which are

labelled with Roman numerals. The BAEP waves I, III and V are the most visible and clinically more significant.[31]

4.9.3. BAEP waves and their site of origin [9, 29, 30, 31]

Wave I- Acoustic Nerve (Eighth nerve)

Wave II-Cochlear nucleus (Medulla)

Wave III- Superior olivary nucleus (Pons)

Wave IV- Lateral lemniscus (Pons)

Wave V- Inferior colliculus (Midbrain)

Wave VI- Medial Geniculate (Thalamus)

Wave V- Auditory Radiation (Thalamocortical)

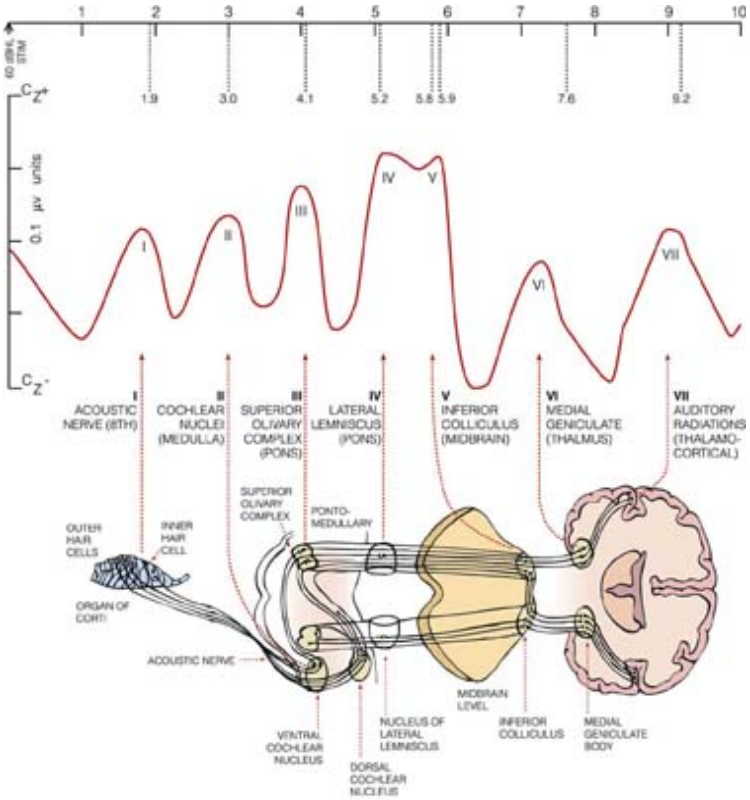


Figure 3: BAEP waves and their site of origin

4.9.4. Analysis of BAEPs [9, 11, 30]

The parameters measured for the analysis of BAEPs are:

1. **Absolute latency:** It is measured in msec from peak of the respective waves.

- **Wave I:** It is a prominent up-going peak in the ipsilateral ear recording channel. It is visible 1.4 ms after the stimulus. It is markedly attenuated or absent from the contralateral ear recording channel.

Clinical significance: Absent in patients with peripheral hearing impairment.

- **Wave II:** It appears as a small peak. It is more prominent in contralateral channel recording.

Clinical significance: Absent in cochlear nucleus lesion.

- **Wave III:** It appears as a prominent peak which is followed by a prominent trough. In contralateral channel recording it appears smaller and earlier than the ipsilateral ear.

Clinical significance: Absent in superior olivary nucleus lesion.

- **Wave IV:** It appears as very small wave in the up going slope of wave V.

Clinical significance: Absent in lateral lemniscus lesion.

- **Wave V:** It is the most prominent peak appearing 5.5 ms after the stimulus. It starts above the baseline and its trough is maximum below the baseline. In ipsilateral recording channel it may fuse with wave IV forming IV-V complex. It mainly derives from connections of the basal turn of the cochlea which subserves the reception.

Clinical significance: Absent in inferior colliculus lesion.

2. **Absolute amplitude:** It is measured in µV from the peak of the wave to the bottom of the trough of wave.

3. **Interpeak latency (IPL):** Commonest used IPLs in clinical practise are I-V, I-III, and III-V.

I-V IPL: It is the difference in latency between wave V and I. It is a measure of conduction from proximal VIII nerve through pons to midbrain. Normal upper limit is 4.5 ms. Slightly shorter in young women and longer in older men. Normal right to left asymmetry should be less than 0.5 ms.It is prolonged in demyelination, ischemia, tumours, brain damage due to ischemia, degenerative disorders, etc.

I-III IPL: It is is the latency difference between wave III and I. It measures the conduction from VIII nerve across subarachnoid space into the core of lower pons. Normal upper limit is 2.5 ms. Normal right to left asymmetry should be less than 0.5 ms. It is prolonged in- tumour or inflammation affecting proximal portion of VIII nerve,meningitis, subarachnoid hemorrhage, Guillain-Barre syndrome, cerebellopontine angle tumors, etc.

III -V IPL: It is the difference in latency between wave V and III. It measures the conduction from lower pons to midbrain. Normal upper limit is 2.54ms. Normal right to left asymmetry should be less than 0.5 ms.

4. Amplitude ratio of wave V/I: Since wave I is generated outside the CNS and wave V inside, these can be compared to determine the relationship of expected signal amplitude. It can be expressed either as ratio or percentage. Normal ratio is between 50% and 300%. Ratio less than 50% suggest central hearing impairment such as multiple sclerosis, hydrocephalous. Ratio higher than 300% suggests peripheral

hearing impairment, high frequency in particular or a sensorineural type. The lower limit of wave V/I amplitude in full-term infants is 30%. The absolute latency and interpeak interval measurements are most widely used parameters clinically.[31]

Table 1: Normal values of BAEP [9]

Wave (latency ms)	**Misra and Kalita**(Mean ± SD)
I	1.67± 0.17
II	2.78 ±0.21
III	3.65±0.22
IV	5.0±0.30
V	5.72±0.3
VI	7.2±0.48
I-III IPL	1.99±0.25
III-V IPL	2.08±0.60
I-V IPL	4.04±0.25

V/I Amplitude Ratio : 0.5-1.3 [35]

4.9.5. Factors affecting BAEP waveforms:

a. Technical factors[25]

1. Stimulus intensity (click)

On decreasing intensity by about 0.03 msec/dB the absolute latencies increase and amplitudes diminishes.

2. Stimulus rate

On increasing click rate the absolute latency of all BAEPs waves increases and amplitude of most of the waves decreases. At higher rates interpeak latencies increase slightly.

3. Stimulus mode

Binaural stimulation produces higher amplitude waves especially III, IV, V at all stimulus intensities than monoaural and binaural stimulation logically produces a higher V/I amplitude ratio than monoaural stimulation at a given stimulus intensity.

4 Filter setting

Filter settings affect relative amplitudes of BAEPs.

5. Site of reference

If reference electrode is kept on the contralateral ear II-III interpeak latency decreases and IV-V interpeak latency increases.

b. Subject factors [25, 29]

1. Age:

The absolute peak latencies of the BAEP waves mainly waves I, III, and V increase with an increase in age. In subjects aged 50 years and older the absolute latencies of Waves I, III, and V are 0.1 to 0.2 ms longer than young adults. The interpeak latencies (IPLs) of the waves I-III, III-V and I-V in the older age groups had an increased value as compared to that in younger individuals.[27, 29, 33]

Females have shorter latency and higher amplitude compared to males. I-V IPL is shorter by 0.1 ms in females compared to males, which may be due to higher internal body temperature, differences in the hormones, and shorter length of brainstem auditory pathway.[9, 29]

2 .Body temperature: [11]

The absolute latency and IPL are prolonged on lowering body temperature. The wave V latency will be slightly prolonged in individuals addicted to alcohol or barbiturates because these agents produce hypothermia.

3. Hearing status: [11]

Hearing impairment can alter the BAEPs, therefore, otoscopic examination, audiometry and hearing tests should be evaluated before conducting BAEP study.

A comparative study of Brain stem Auditory Evoked Potentials in 25 preterm and 25 full-term infants done by M.S Roopakala et al showed a prolongation in latency of wave V in preterm infants and suggested reason for this as retarded

myelination of the central auditory pathway. They concluded that electrophysiological tests like BAEP could be used to assess neuronal maturation and myelinaton in preterm infants.[36]

Auditory evoked potential study done by Maria Khatoon et al inDepartment of Physiology, Peoples College of Medical Sciences, Bhopal, India, in twenty five normoacoustic elderly subjects & twenty five age and sex matched controls (young adults between 18-25 years age group) showed prolonged wave III & wave V latencies in older adults as compared to the young adults . The interpeak latency I-III and I-V are also prolonged which suggest that aging process is central phenomenon.[27]

A study done by Harinder J S et al., Government Medical College, Amritsar, to find the age and sex related changes in the brainstem auditory evoked potential in 150 normal healthy subjects of different age groups (G1 = 15-29 years, G2 = 30-45 years, G3 = 46 years onwards), with a matched number of males and females in each group showed that the absolute latencies of the waves III, IV and V significantly increases and interpeak latency of the waves, I-III and I-V also increases with increasing age, thus suggested degenerative changes in the auditory pathway and synaptic delay.The latencies of the waves III, IV and V and interpeak latencies of the waves, I-III, I-V and III-V are significantly increased in males as compared to the females. Thus suggests age and sex have an effect on latency and interpeak latency in Brainstem auditory evoked potentials.[29]

Another study on Brainstem evoked response audiometry done byMaria Carolina Braga NorteEsteves et al on sixty normal hearing subjects aged 9 and 66

years showed statistically significant difference in wave latencies between males and females and no difference found between ears.[31]

A study onage and gender effects on Auditory Brain Stem Response done by YonesLotfi et al on 120 subjects (60 males and 60 females) of three age groups: 18-30, 31-50 and 51-70 years old, at a Rehabilitation Center in Tehran, Iran. Examined the age and sex influences on wave I and V absolute latency, and I-V IPL and showed that significantly shorter latency of wave I, V, and IPL I-V latency in females than males.The latency of wave I, V and IPL I-V in the 51-70 year old group was significantly higher than the 18-30 and 31-50 year old groups.[33]

4.9.6. Clinical neurophysiological correlation: [9]

Although the changes in BAEPs are nonspecific, they provide information about the function of corresponding auditory pathways. So the abnormalities in BAEP should be correlated with the clinical picture and other investigations.

4.9.7. Clinical applications of BAEPs: [9, 26, 31]

The most important clinical applications are to establish a minimal auditory response level, to assess the maturity of the central auditory system in neonates, to characterize the type of hearing loss, to assess the type and level of hearing loss in children below 5 years of age, to monitor surgery of the posterior fossa, to assess balance disorders, to define the site of auditory nerve or brainstem injury, to assess metabolic, demyelinating and degenerative diseases and to monitor patients in intensive care units and as a prognostic predictor of coma and determination of brain death and to detect cerebellopontine angle tumors, intrinsic brainstem tumors, multiple sclerosis, to follow -up after operations concerning brainstem etc.[31]In the

evaluation of suspected retrocochlear pathology ABR audiometry is used as an effective screening tool.[9]

4.9.8. Abnormal BAEPs [11]

1) Absence of wave I :

Causes: Large tumor damaging VIII nerve, VIII nerve ischaemia.

2) Absence of wave beyond wave I :

Causes: acoustic neuroma, meningioma, demyelinating disorders

3) Absence of waves IV and V :

Causes: multiple sclerosis, hydrocephalous

4) Right to left latency asymmetry more than 0.5 msec is seen in acoustic neuroma

4.9.9. Effect of ovarian hormones on auditory system: [37]

In addition to the regulation of reproductive behaviour, ovarian hormones regulate the activity of hypothalamic and extrahypothalamic noradrenergic, dopaminergic and serotonergic neurons.

Role of Estrogen:

Several studies have shown the effect of estrogen on the processing of hearing in humans, and this effect, in part, is thought to result from regulation of the transcription of genes via their classical estrogen receptor (ER) pathway. The actions of estrogen are mediated by estrogen receptors alpha and beta (ERα and ERβ), which act as transcription factors and are belongs to the nuclear receptor superfamily. [14]In the inner ear of humans and animal models (rat and mice), estrogen receptors alpha

(ERα) and beta (ERβ) have been identified mainly in spiral ganglion type I cells, the striavascularis and cochlear blood vessel.[38]

Estrogen receptors are also present in the outer and inner hair cells. This suggests that estrogen may influence auditory transmission. The receptors in the striavascularis may regulate the fluid and electrolyte balance in the cochlear fluids. The cochlear blood vessels contain receptors for estrogen, this may influence auditory function by modulating cochlear blood flow.[37]

A study done by K. Charitidia et al in the Department of Physiology and Pharmacology, Sweden onthe expression of estrogen receptorsin the brain areas related to hearing in prepubertal and aged mice showed that the estrogen receptors are present throughout the central auditory system in different periods of maturation suggests that by regulating the transcription of genes via their classical estrogen receptor pathway, estrogen directly affect the processing of hearing in humans.[14]

A study done by Thompson and colleagues demonstrated that 3 months treatment with tamoxifen showed auditory function changes in young adult female CBA mice. They also found that there is a decrease in suppression of distortion product otoacoustic emissions (DPOAEs) on blocking ER. This may be due to a reduction of the Medial Olivocochlear system (MOC) suppression. This decrease is same as that occurring in aging and before the onset of age related hearing loss and they suggest that in addition to its neuroprotective effect, estrogen was found to have a protective role on auditory function. One of the mechanisms involved in this

protective effect may be the “genomic” action of estrogen on its membrane receptors-alpha and beta.[37]

Role of Progesterone:

Progesterone acts as a neurosteroid. Studies done in rat showed the presence of progesterone receptors within the inner ear such as the endolymphatic sac and striavascularis. By regulating endolymph and cochlear blood supply these structures play essential roles in underlying hearing mechanisms.[39]Progesterone may cross-react with other steroid receptors present in the cochlea or more proximal areas of the auditory system. GABA-A receptors are present throughout the auditory system. Progesterone and its metabolites act as GABA-A agonist and interact with the steroid binding sites on these receptors. By this way progesterone may affect the auditory system. It may affect auditory processing indirectly by decreasing the 5-HT levels.[37]

4.9.10. Auditory Evoked Potential in different phases of menstrual cycle:

Conflicting studies are there regarding hormonal changes during menstrual cycle and the changes inAuditory Evoked Potential.Caruso et al., and Serra et al., reported shorter BAEP latencies during the periovulatory phase ofthe female sexual cycle and they suggest the reason for this as the high estrogen level in this phase.Stomati et al., showed that when the OVX rats are treated with estrogen there is a dose dependent increase in level ofallopregnaloneboth centrally and peripherally. According to Disney and CalfordGABA inhibition in the auditory pathway in the midbrain may get facilitated by an increase in neurosteroids (such as allopregnalone). In the luteal phase the ABR latency changes are due to the action of progesterone.[37]

A Brainstem Auditory Evoked Potentials (BAEP) study conducted by Navapreet Mann et al.,Maulana Azad Medical College, New Delhi, on 50 young females of age group19-36 years, during four different menstrual cycle phases showed a significant increase in the waves, I to V peak latencies in the oestrogen peak mid cycle and a significant decrease in the same during progesterone peak mid-luteal phase. IPL did not show any statistically significant change in the above two phases. No significant changes occurred in the menstrual and the pre-menstrual phases. They suggests, BAEP changes in the mid follicular and the mid luteal phases of the menstrual cycle are attributable to the changes in oestrogen and progesterone during the cycle.[7]

A study on Brainstem Auditory Evoked Potentials (BAEP) done by SandeepKaur et al., Adesh Institute of Medical Sciences & Research, Bathind, Punjab on 40 regular menstruating healthy females of age group 19 to 23years in three different menstrual cycle phases showed statistically significant increase in waves I, III and V absolute latencies in proliferative phase as compared to menstrual phase and a statistically significant decrease of the same parameters in secretory phase as compared to proliferative phase. They suggests that the central auditory conductivity is affected by the hormonal changes during menstrual cycle.[40]

A Brainstem auditory evoked responses (BAERs) study done by R Howard et al., University of Otago, Dunedin, New Zealand on 21 healthy control women and 30 women diagnosed to have Late Luteal Phase Dysphoric Disorder (LLPDD) in three menstrual cycle phases showed no change in BAEP latencies in healthy control women at different menstrual cycle phases, increased wave III BAEP latency in

females with moderate PMS symptoms compared to healthy controls and an increased waves III and V BAEP latencies in women with severe PMS symptoms compared to healthy controls.[41]

A Brainstem auditory evoked responses (BAERs) study done in three different menstrual cycle by Salvatore Caruso et al on 94 women after the third month of oral contraceptive intake showed decrease in wave latencies and inter-peak intervals during the periovular phase as compared to the luteal phase. They suggested BAEP seems to be depend on the hormonal variations that occur in each menstrual cycle and also during oral contraceptive intake.[42]

Auditory Evoked Potential study done by A. Zani from the Instituto di Psicologia del C.N.R., Rome, Italy on eight young female athletes of age group 20 to 24 years who were undergoing regularly and intensively training in different sports , of which four are on oral contraceptives and four without oral contraceptives showed a constantly increasing delay in wave V latency on moving from menstrual phase to midcycle (ovulatory phase) and sharp decrease in the same in premenstrual days.They suggested this may be due to the neurofunctional interactions between different level neural structures and gonadal steroid hormones.[32]

A study on auditory brainstem response (ABR) was done by NamrataUpadhayay et al., on 40 healthy female volunteers of age group19 ± 2.35 years. The ABR latency of wave V, IPL III–V and I–V were shorter in postovulatory phase as compared to the preovulatory phase. They concluded that compared to

preovulatory phase ABR is better in postovulatory phase, this may be due to the effect of progesterone in this phase.[43]

A Long latency auditory evoked potential study was done by AshaYadav et al., University College of Medical Sciences & GTB Hospital, Delhi on 20 females having normal ovulatory menstrual cycles and twenty control females of same age group having anovulatory menstrual cycles on oral contraceptive (O.C.) pills, across the four different menstrual cycle phases. They proved that the central processing of the auditory informationis modified by the variations in estrogen and progesterone in a normal cyclic female .[44]

A study on auditory brainstem responses (ABR), mid-latency responses (MLRs) and slow vertex responses (SVRs), done by AshaYadav et al., University College of Medical Sciences & GTB Hospital, Delhi on 20 women in four different menstrual cycle phases showed that in estrogen-peak mid-cycle there is an increase in peak latencies of ABR waves III and V and IPL I-V, and in progesterone-peak midluteal phase there is a decrease in latencies. Peak latencies of MLR waves also show a same trend. In the mid-cycle there was a significant decrease in SVR waves P2 and N2 while conduction is faster in midluteal phase.All the waves showed shortest latencies during menstruation. They suggest that during the menstrual cyclethe ovarian steroids are modulating the whole auditory neural conduction and the effects are better visible on the central component.[45]

4.10. Visual Evoked Potential (VEP)

In 1930s the changes evoked by visual stimuli were recorded directly from the surface of the pia mater in animals for the 1st time.[28]

Visual Evoked potential (VEP) is one of the electrophysiological technique which is used by neurophysiologist, ophthalmologist, and neurosurgeons for better diagnosis of optic nerve fibre and visual cortex diseases such as Multiple Sclerosis, Optical neuritis etc.[46]The electrical potential differences recorded from scalp in response to visual stimuli is known as Visual Evoked Potential (VEP). It represents a resultant response of cortical as well as subcortical areas to photostimulation. It assess the optic nerve conduction up to the visual cortex "area 17". VEPs are one of the most useful tool in testing optic nerve function.[25]VEPs depend on functional integrity of central vision at any level of the visual pathway including the eye, retina, the optic nerve, optic radiations, and occipital cortex.[47] Many neurological disorders present with visual abnormalities and detection of subclinical lesions affecting the visual system which are poorly visualized by MRI or in unreliable clinical examination or ruling out of psychogenic origin, depends mainly on the VEPs.[28]

The Visual Evoked Potentials or the Visual Evoked Responses are the evoked potentials produced when the retina is stimulated with light (flashes/pattern stimulation) and the potentials are generated in the cortical and sub-cortical visual areas and best recorded over the occipital region. It is a very important non-invasive tool in detecting visual system abnormalities.[28]

4.10.1. Anatomical basis of Visual Evoked Potential:

On exposure to light, the photoreceptors, rods and cones get stimulated. These receptors synapse with bipolar cells then with the ganglion cells. The axons of ganglion cells form the optic nerve. The optic nerve is about 5 cm long and it extends from the retina to the optic chiasma. About 1million optic nerve fibres are unmyelinated in the retina and in the optic nerve head, but get myelination as these pass through the optic chiasma located above the sellaturcica. The optic nerve fibres primarily carry visual impulses and also impulses for accommodation and reflex response to light and other stimuli. The fibres from temporal half of the retina are located in the temporal half of the nerve and it pass through the chiasm without crossing to the opposite side and continue to the ipsilateral reflex centres for pupillary reaction and ipsilateral visual areas. The optic nerve fibres from the nasal half of retina pass through the medial portion of nerve, cross at the chiasm and terminate at the contralateral cortex. In the optic chiasm, the fibres from upper retinal quadrant occupy dorsal and those from the lower retinal quadrant occupy ventral areas. The fibres associated with central vision coming from macula form papillomacular bundle in the peripheral portion of optic nerve. As the nerve approaches the chiasma the papillomacular bundle approaches the centre of the nerve and the temporal fibres are lateral. The fibres from the medial half of the macula decussate, but not the lateral. From optic chiasma optic tract starts and end in lateral geniculate body. The optic tract consists of ipsilateral temporal and contralateral nasal retinal fibres. From the optic tract fibres responsible for pupillary reflex pass to EdingerWestphal nucleus. The fibres carrying impulses from upper portion of retina terminate in ventromedial segment and the lower portion in ventrolateral segment of lateral geniculate body. The

macular fibres occupy an intermediate position in the dorsal, middle and caudal portion of lateral geniculate body. In the lateral geniculate body, the ipsilateral temporal and contralateral nasal retinal fibres alternatively terminate in six layers. From here the neurons form optic radiation terminate in striate cortex (area 17).The macular fibres end in the occipital lobe at the pole in a wedge-shaped area. The upper half of retinal fibres relay superior and the lower half inferior to the calcarine fissure.

The P100 waveform of VEP is generated in the striate and peristriate occipital cortex. It occurs due to activation of primary cortex and thalamocortical volleys. On giving pattern or flash stimulation the metabolism in primary visual area and visual association areas (area18 and 19) increases. The regional cerebral blood flow increases with stimulation rate up to 8 Hz and gradually declines thereafter. Recently, the origin of first major component of VEP on pattern shift stimulation has been reported to originate from primary visual cortex.

The retinal ganglion cells are classified into X and Y cells. The X cells are small retinal ganglion cells with small diameter axons. They mediate cone vision with lateral inhibition. They have a small receptive field and distributed in the central part of retina. They have low sensitivity to motion and provide substrate for pattern shift VEP (PSVEP) via geniculate pathway. Thus they are useful in assessing the visual acuity.

The Ycells are large retinal ganglion cells with large diameter axons. They mediate rod vision without lateral inhibition. They have a large receptive field and distributed in the peripheral part of retina. They have high sensitivity to motion and

provide substrate for flash VEP via extra geniculate pathway. Thus they determine the presence or absence of light perception.

VEP primarily reflect the activity originating in the central 3º to 6º of visual field which is relayed to the surface of occipital lobe. The projections arising from the peripheral retina are directed to the regions deep within the calcarine fissure, hence unrecordable on peripheral retinal stimulation.[9]

4.10.2. Types of VEPs:

1. **Transient VEP**: Stimulus given at a relatively low rate (up to 4/s) 1Hz produce the reversal pattern every 500 msec.[11, 48]

2. **Steady state VEP**: Stimulus is given at higher rates (10/s or higher) 4-8Hz.The steady state VEP are repeated evoked potentials which constitute discrete frequency components and remain constant in amplitude and phase over long period of time.

3. **Pattern VEP**: This was developed and popularized in the early1960s.[28] Responses elicited by patterned stimuli are called “pattern” VEPs or PVEPs.

Compared to unpatterned stimuli, patterned visual stimuli evoke responses show less intra- and inter individual variability. With this even minor visual pathway abnormalities can be detected with much greater sensitivity and accuracy as compared to Flash VEP testing.[48]

The most frequently and widely used pattern stimulus to assess visual pathway defects in clinical investigations is checkerboard pattern reversal because they elicit relatively large potentialsand it is more sensitive to the visual pathway conduction abnormalities. It is estimated that 65% of the pattern-reversal response is generated in

fovea.[25]The checks alternate from black to white and vice versa at every 1 or 2 seconds. Each alternation acts as stimulation and produces an evoked potential at the occipital lobe.[49]It is an useful clinical tool in the diagnosis and documentation of visual impairment in pediatric and adult neurologic disorders.

4.10.3. Characteristics of pattern reversal stimulation [25]

In 1980 Erwin outlined 7 basic characteristics of pattern-reversal stimulation:

1. Rate of pattern-reversal: It is the number of times that the pattern changes within a second. Usually all the pattern reversal responses are averaged together.
2. Reversal time: It is the total time taken to change from one pattern to its opposite.
3. Stimulus luminance is an important attribute for visual stimulus.
4. Type of the pattern used is very important. Checkerboard stimulus is most commonly used.
5. Orientation of the pattern: Vertical-horizontal orientation elicit larger responses as compared to oblique orientation.
6. Size of the pattern elements: It can be described in two ways. The visual angle subtended by each element can be measured. Also, the spatial frequency can be used.
7. Another aspect is the spatial rate of luminance change. Field size and relationship to fixation are the most important aspects of the stimulus .[25]

4.10.4. Normal Pattern Shift Visual Evoked Potential (PSVEP):

A high contrast black-and-white checkerboard spanning the central 20˚–30˚ of the visual field is used as the visual stimulus. The black and white squares periodically exchange places. The averaged response to this reversal is considered as VEP.[26]

In normal subjects, the pattern reversal evoked potential to full field stimulation consists of three peaks.[25] Two negative waveform denoted as N and the positive waveform as P, which is followed by the approximate latency in milliseconds. The commonly used waveforms are N_{70}, P_{100} and $N_{135.}$ The subscript number denotes the time in milliseconds after stimulation.[11]

A prominent positive wave (called P100), appears almost 100 ms after the pattern reversal, this signal is picked up by the midline occipital electrode normally. The waveforms at the lateral electrodes are variable and the midline electrode shows the latency of P100 so it is taken as the measure of retino-striate conduction time.[26]

The measurement of P_{100} peak latency, its duration and amplitude for VEP analysis is most commonly used. P100 latency is least affected by technical factors and degree of patient cooperation and its prolongation is the most reliable indicator of clinically significant abnormality.[48]

4.10.5. VEP waves and their site of origin:

P_{100} waveform generated in the striate and pre-striate occipital cortex, due to activation of primary visual cortex and thalamocorticalfibers discharge.[25]

The VEP is primarily a reflection of activity originating in the central 3º to 6º of the visual field as the retinal projections from this area is relayed to the surface of the occipital lobe while those from the peripheral areas are directed to deeper regions within the calcarine fissure. Therefore, when scalp electrode picks up the signals directly from the cortical tissue that receives the central inputs. VEP is mainly a reflection of the cone activity.[9]

On giving visual stimuli, there is increased metabolism in the primary visual area and also in the visual association areas 18 and 19.The cerebral blood flow is found to increase with increase in stimulation rate up to 8 Hz but declines gradually thereafter. Using intracerebral recording in awake humans, it is found that P100 appears to be generated by the pyramidal cells in layer IV of area 17. According to the imaging studies the source of the early phase of the P100 peak appears to be in dorsal extrastriate cortex of the middle occipital gyrus, whereas the late phase of P100 generated by the ventral extrastriate cortex of the fusiform gyrus. These results suggest the cortical generation of VEP waveforms.[28]

N_{70} waveform – reflects the activity in the fovea and primary visual cortex.[11]

N_{135} waveform – reflects the activity in the visual association area 18 and 19.[11]

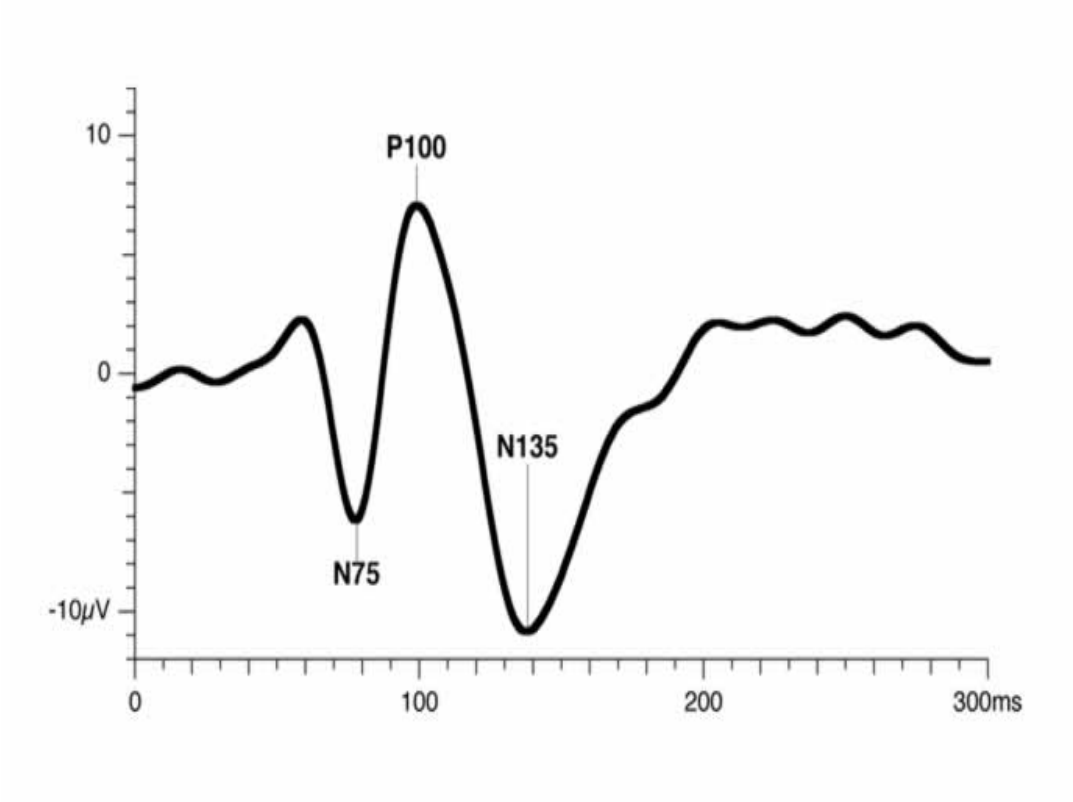


Figure 4: Visual Evoked Potential Waveform

Table 2: Normal values ofVEP: [9]

Parameters	**(Mean ± SD)**
P_{100} Latency (ms)	96.9 ±3.6
R-L (ms)	1.5±0.5
Amplitude (μV)	7.8 ±1.9
Duration	55.9 ± 7.7

4.10.6. Factors affecting VEP (P_{100} waveform)

a. Technical factors [25]

1. Screen luminance: P100 latency increase with decrease in brightness. The pupillary diameter also affect P100 latency , as this has an effect on retinal illumination. Decrease in area of retinal illumination reduces the amplitude and increase the latency of VEP.

2. Degree of contrast: On reducingthe degree of contrast between the black and white squares of checkerboardpattern P100 latency increases and amplitude reduces.

3. Size of the stimulating pattern: When the size of the stimulating pattern (degree of visual angle) decreases the amplitude of the response decreases .

4. Check size: Smaller checks will produce highest amplitude responses.

5. Electrode placement: More anterior placement of electrodes results in shorter VEP values.

6. Stimulus rate

When the stimulus rate is increased beyond 8 per second, the evoked responses will change to steady state evoked potential.

b. Physiological factors [25, 50, 51, 52]

1. Age: In young children and infants, the P_{100} latency on large checks reaches the adult value by 20 weeks and the latency on smaller checks takes 5-6 years to reach the

adult value. This is due to the age related changes in retina and the rostral part of visual system. The mean amplitude is almost double of adult value in the first decade of life

2. Sex: Latency is larger in males compared to females. This may be due to large head size and low core temperature of the body in males. The mean amplitude is higher in females compared to males, probably due to hormonal differences.

3. Eye dominance: Shorter latency and higher amplitude of P_{100} wave obtained on stimulating the dominant eye compared to the non dominant eye.

4. Hemispherical dominance: The amplitude of P_{100} wave is greater in right hemifield stimulation in right handed individuals due to neuroanatomic asymmetries of human striate cortex.

5. Occular movement: The amplitude of P_{100} wave is reduced by eye movement.

6. Visual acuity: The latency and amplitude remains normal with visual acuity as low as 20/120, however the amplitude decreases with further decrease of visual acuity.

7. Mental activity: Decrease latency and increase amplitude of P_{100} waveform.

8. Drugs: P_{100} latency increases with use of miotics and decreases with mydriatics. Carbamazepines prolong VEPs.

9. Serum glucose level: P100 latency increased with increasing serum glucose level, with a 6.9% estimated latency difference between lower and higher glucose concentrations.[25]

A study done by Anju Thakur Jha, ParveenSiddiquiYousuf andSwarnaBiseria Gupta, LN Medical College & Research Center, Bhopal, to find the effect of myopia on visual evoked potential on 130 healthy volunteers of age between 17-21yrs of both sex, grouped as without refractive error N=69 (F=36 & M=33) and with refractive error N=61 (F=31 & M=30) showed statistically highly significant difference in latency of P100 between both eyes in group with refractive error and N75-P100 amplitude difference also shown high statistical significance in the group with refractive error.[51].

A study done by Ruchi Kothari et al in Department of Physiology, MGIMS, Sevagram, Wardha, Maharashtra to find the effect of refractive errors on visual evoked potentials showed that prolonged P100 latency and reduced amplitude with refractive errors. They concluded that the VEPs seem to be more affected by myopia than hypermetropia.[52]

4.10. 7.VEP abnormalities: [11]

1. Prolongation of latency: Commonest cause is demyelination in optic pathways. This results in delayed conduction in the visual pathway.

Causes: multiple sclerosis, optic neuritis (alcoholism, vitamin B_{12} deficiency, tobacco), glaucoma.

2. Reduction in amplitude: Axonal loss due to ischaemic optic neuropathy produces reduction in amplitude of P_{100} waveform.

Causes: Hypertension, CNS vasculitis refractory errors, media opacities, and retinal diseases.

3. Both amplitude and latency abnormalities: Optic nerve compression produces segmental demyelination and axonal loss resulting in increase in latency and reduction in amplitude.

Causes: Severe papilloedema, pituitary tumour.[11]

4. Shape abnormalities: Bifid pattern of P_{100}, that is two peaks separated by 10-50 msec, get in visual field defects. This may be due to shifting of transitional zone.

4.10.8. Physio-clinical significance of VEP:

In uncooperative subjects where fundus examination is not possible VEP testing is necessary.VEP provide an objective and sensitive information of abnormalities in visual system especially anterior to optic chiasma.[9]

4.10.9. Clinical usefulness of VEPs:

The major use of VEPs is in the detection of sub-clinical lesions within the visual system; asymptomatic optic neuritis is easily detected and its presence may aid in the diagnosis of MS. VEPs an important adjunct when the diagnosis of demyelinating disease is in doubt, as the optic nerve abnormalities are poorly visualized by MRI. A normal VEP excludes significant optic nerve or anterior chiasmatic lesion thus it helps to assess patients with subjective complaint of visual loss. It will also help to distinguish blindness from hysteria and malingering: if a patient reports visual loss, a normal VEP strongly favors a psychogenic disorder.[28]

In infants, VEPs has been used to assess integrity of the visual system when blindness is suspected and also to detect unilateral amblyopia at an early age when recovery may still be possible.[28]

VEP is useful in the diagnosis ofMultiple sclerosis, Optic Neuritis, Ischemic Optic Neuropathy, AIDS-related ocular lesions, Toxic amblyopia, Glaucoma, Retrobulbar neuritis, Tumors compressing the optic nerve, Vitamin B_{12} and E deficiency, Malingering and hysteria, Intra-operative monitoring in pituitary and cavernous sinus tumor. [25, 26]

4.10.10. Effect of ovarian hormones on Vision:

In young females, the retina and retinal pigment epithelium (RPE) of eyes showed 65-kDa ERα protein. ERα is also detected in the ciliary body, iris, and in the epithelium of the lens.[23]Various studies reported that estrogen increase the sensitivity of receptors in the optic pathways to dopamine and thereby decreases the visual transmission time. [50]

4.10.11. VEP studies in menstrual cycle:

A study done by Luiz Antonio De Lima Resende et al, in Department of Neurology and Psychiatry, State University of São Paulo (UNESP) on pattern-shift visual evoked potentials (PS-VEP) in 20 female volunteers of ages 23 to 26 years at different menstrual cycle phases showed decreased latencies for P100 (PS-VEP) wave in the progesterone phase..[13]

A study done by Yasuhiro Kaneda et al in the Department of Neuropsychiatry, Japan on visual evoked potential (VEP) and electroencephalogram (EEG) changes in the menstrual cycle in regularly menstruating healthy females, with 21 at the follicular phase (FP) and 23 at the luteal phase (LP) showed that the VEP and late EEG changes at LP reflect the effect of progesterone more than estrogen.[53]

A study done by ParveenSiddiquiYousuf and Anju Thakur Jha in LN Medical College & Research Center, Bhopal, to find the effect of phases of menstrual cycle on visual evoked potential on 40 healthy female volunteers of age between 17-21yrs with regular menstrual cycle tested on follicular and luteal phaseshowed that prolongation of P100 latency during luteal phase.[50]

A Visual Evoked Potential study done byMohsen Azarmina, MasoudSoheilian, HosseinAzarmina, and ShahidBeheshti, University of Medical Sciences, Iran, on15 females of age 18 to 25 years in the follicular phase and luteal phase showed prolonged VEP latency in the luteal phase .[54]

A Pattern reversal Visual Evoked Potential study done by Sangeeta Gupta et alon20 women of age group18-25 years, in the menstrual cycle phases (proliferative and luteal phases) showed statistically significant reduction in mean P100 PRVEP latency in the proliferative phase as compared to the luteal phase and a statistically insignificant increase in N75-P100 amplitude in the luteal phase.[55]

MATERIALS & METHODS

5. MATERIALS AND METHODS

5.1. Study design:

This study was designated as cross sectional study.

5.2. Study setting;

The study was conducted in Department of Physiology, SreeMookambika Institute of Medical Sciences, Kulasekharam (Kanyakumari District), Tamilnadu.

5.3. Study period:

This study was done during the time period from January 2014 to April 2015 for over a period of 16 months.

5.4. Sampling technique: Non randomized purposive sampling method.

5.5. Scientific basis of sample size used in this study:

The sample size of this study was determined based on the studies published in literature.

The formula used is $n= (u+v)^2 \times (SD1^2+SD2^2)/(\mu1-\mu2)^2$

u=0.84 for 5% level of significance.

v=1.96 for 80% power.

According to previous study done by Mann et al[7] the Standard deviation 1(SD1) is 0.22, Standard deviation 2 (SD2) is 0.23,Mean 1 (μ1) is 5.62 and mean 2 (μ2) is 5.52.

SD1=0.22

SD2=0.23

μ1=5.62

μ2=5.52

Hence by applying the formula,

$n = (0.84+1.96)^2 \times (0.22)^2 + (0.23)^2 / (5.62-5.52)^2$

$= 7.84 \times (0.0484+0.0529)/(0.1)^2$

$= 7.84 \times 0.1013/(0.1)^2$

$= 7.84 \times 0.1013/0.01$

$= 0.794192/0.01$

$= 79.4192$

5.6. Study group:

This study was conducted in 80healthy female nursing students of age18-20 years with regular menstrual cycle and normal Body Mass Index.

5.7 Inclusion criteria:

1. All first year Female Nursing Students of SMIMS with regular menstrual cycle (lasting 28 – 32 days.)

2. Age group: 18-20 years.

3. Body mass index: 18-25kg/m^2

4. Femaleswith normal visual acuity.

5.8. Exclusion criteria:

1. History of irregular periods.
2. History of drug intake (eg: hormonal pills, steroids, anti-depressants, neuroactive substances etc)
3. History of dysendocrinism, metabolic or neoplastic pathologies.
4. History of chronic illness, neurologic or psychiatric illness.
5. Auditory defects (eg: conductive hearing loss, sensorineural hearing loss).
6. Visual defects (eg:colour blindness).
7. Pregnancy, lactation.

5.9. Parameters to be studied

BRAIN STEM AUDITORY EVOKED POTENTIAL (BAEP)

Peak latencies (Milli Second), of the waves I,II,III,IV and V , inter peak latencies of I- V, I-III and III- V, and the amplitude ratio(V/I).

VISUAL EVOKED POTENTIAL (VEP)

P_{100} peak latency (Milli Second) and amplitude (micro volt)

5.10. Methods /Instrument:

The instrument used for the study was computerized RMS ALERON 401 EMG/NCV/EP measuring system designed for any neurophysiological application. The instrument was supplied by records and Medicare systems Pvt. Ltd. Chandigarh, India.

5.11. Institutional Human Ethical Committee (IHEC) Approval :

Before conducting the study, the study proposal was submitted to the Institutional Human Ethical Committee (IHEC) of SreeMookambika Institute of Medical Sciences (SMIMS) Kulasekharam, K.K District, Tamilnadu, for approval and same was approved by the Institutional Human Ethical Committee SMIMS with Ref. No. SMIMS/IHEC/2013/C/06.The certificate of approval has been enclosed in annexure.

5.12. Procedure in brief:

After getting the approval from Institutional research committee (IRC) and Human Ethical Committee (HEC),written informed consent was obtained from all the volunteers before enrolling them into the study.

The study was conducted in the department of physiology. 80 female first year nursing students of age 18-20 years with regular menstrual cycle (lasting 28-32 days) was selected. The subjects with normal body mass index (18 -25kg/m^2) and those who were not taking any hormonal pills during the past 6 months were included in this

study. A detailed menstrual history was taken from each subject. Before conducting the BAEP and VEP, a priliminary selection tests on hearing, vision and anthropometric data was taken. Tuning fork tests like Rinne's and Weber's test and otoscopy was performed to exclude any conduction defect. Snellen's chart, Jaeger's chart and Ishihara's chart testing was done to exclude decreased visual acuity and colour blindness.

During their menstrual cycle each women was subjected to three brain stem auditory evoked potential (BAEP) and visual evoked potential (VEP) testings, the first at the menstrual phase (day 1-4),the second at the proliferative phase (day 5-14), the third at the secretory phase (day 15-28).[56] The day of ovulation was found out by the basal body temperature chart and a retrospective calculation was done from the day of onset of the next menstrual cycle. Before conducting the BAEP and VEP tests, each subject was seated comfortably in an arm chair in an electrically and acoustically shielded room with dimmed light. The subjects were briefed about the procedure and asked for their co-operation throughout the procedure. To avoid the postprandial drip in sensory perception and performance and diurnal variation, the tests were conducted between 10 and 12 am.

Pre-test instructions:

- The subjects were asked to shampoo wash their hair on the previous day of the test and to avoid hair chemicals, oils and lotions.
- Advised to avoid intake of drugs or foods containing caffeine on the day and the previous day of the test.
- Advised to take adequate sleep on previous night.
- Subjects were restricted from use of sedatives, miotic or mydriatric drugs on the day and the previous day of test.
- They are asked to wear the spectacles or contact lenses during the test if using, to prevent refractive errors.

Brainstem Auditory Evoked Potential (BAEP) Maneuver: [11]

By using electrode paste the recording (active) electrodes were pasted on the mastoid process of both ears, reference electrode at vertex Cz and the ground electrode in front of the vertex that is at the Fz according to the 10–20 international system of EEG electrode placement. The site of application was cleaned with an abrasive cleanser (spirit) before the electrode placement. All electrodes were plugged to a junction box and skin to electrode impedance was kept below 5 Kohm. 2000 click stimuli which had an intensity of 70dB above the normal hearing threshold were given to each ear seperately, at the rate of 11.1/sec and for a duration of 0.1 ms. The stimulation was of the rare-type, with a linear envelope. The sweep speed was 1ms/division and the sensitivity was 0.5μV/div. These clicks were generated by passing 0.1 ms square pulses through shielded headphones. Contralateral

(nonstimulated) ear was masked by white noise at 40 dB SPL to eliminate “crossover” responses, i.e., bone-conducted responses originating in this ear. The low cut filter was set at 100 Hz and high cut at 3 kHz.Signals picked up by electrodes were filtered, amplified, averaged and displayed on the screen ofBERA machineand hard copy of the recordings were taken. A series of five waveswere recorded during the first 10 ms after giving the auditoryclick stimulus. The peak latencies of the waves, I, II, III, IV and V, the inter peak latencies of I-V, I-III and III-V, and the amplitude ratio (V/I) were recorded. Both the ears of each woman were treated as separate samples and thus, the ABR wave forms were analyzed separately for each ear.

Visual Evoked Potential (VEP) Maneuver: [11]

The subjects were seated comfortably 100 cm away and in front of the monitor. By using electrode paste the active electrode was pasted on the occiput (Oz), reference electrode was kept at about 12 cm above the nasion (Fpz) and the ground electrode over the vertex (Cz) according to the 10–20 international system of EEG electrode placement. The site of application was cleaned with spirit before the electrode placement. All electrodes were plugged to a junction box and skin to electrode impedance was kept below 5 Kohm. The visual stimuli were alternate black and white checkerboard patterns (contrast 70%, mean luminance 50 cd/m2) generated on a video monitor. The check edges subtend a visual angle of 15 minutes with video monitor screen subtending an angle of 12.5°. The subjects were asked to fixate their one eye (other being closed with a patch) on the central spot of the TV monitor. Each eye was tested separately (monocular testing). The reversal rate of checks is kept as twice per second. Every time the pattern alternates, the subject's visual system

generates an electrical response that was detected and recorded by surface electrodes. 300 stimuli was given at the rate of 1.71/sec and for a duration of 500ms. The sweep speed was 30ms/division and the sensitivity was 5μV/div. The low cut filter was set at 2 Hz and high cut at 100 Hz.Signals picked up by electrodes were filtered, amplified, averaged and displayed on the screen ofVEP machineand hard copy of the recordings were taken. P100 peak latency and amplitude was recorded. Both the eyes of each female were treated as separate samples and thus, the VEP wave forms were analyzed separately for each eye.

After completing the BAEP and VEP recordings in all the three menstrual cycle phases, the hard copies of the same were maintained in separate files and the results obtained were analysed with standard normal values.

5.13. Statistical methods of analysis:

1. P value <0.05 was considered as statistically significant.
2. The statistical analysis was done by using one way ANOVA Posthoc test followed by Dunnet t test with the statistical parameters like mean and standard deviation.
3. Data was entered in Microsoft excel 2007 office and was analyzed using statistical software SPSS – 16.0.version.

RESULTS

6. RESULTS

6.1. Study subjects:

In the present study, total 80 subjects were recruited after considering inclusion and exclusion criteria. They were tested in three different menstrual cycle phases. The baseline characteristics of the study subjects have been depicted in the table 3and 4.

Table-3: Distribution of subjects based on the Age data

Age (Years)	Number	Percentage (%)
18 years	61	76.25
19 years	19	23.75
(MEAN±SD)	**18.23±0.43**	**100**

Table-4: Distribution of subjects based on the BMI data

Body Mass Index	Number	Percentage (%)
18-20	52	65.00
21-23	20	25.00
Above 23	8	10.00
(MEAN±SD)	**20.38±1.61**	**100**

6.2.Assessment of latency changes in Brainstem Auditory evoked potential (BAEP):

The study showed statistical significant decrease in latency of BAEP wave V on the right side ($p < 0.05$) and also in the left side ($p < 0.05$) during proliferative phase (phase 2) of menstrual cycle as compared to secretory phase (phase 3) and an increase in latency of the same wave during secretory phase (phase 3) as compared to menstrual phase (phase 1). The latencies of waves I, II,III and IV showed the same trend but statistically insignificant. There is no significant difference in the latency changes of BAEP on the right side when compared to the left side ($p > 0.05$). The latency changes during different phases has been depicted in the table 5, 6 and 7.

Data are represented as Mean ± SD

BAEP: Brainstem Auditory Evoked Potential

Number of subjects: 80 in each phase

Phase -1: Menstrual phase

Phase -2: Proliferative phase

Phase -3: Secretory phase

$p < 0.05$ is significant

Data are analyzed by one way ANOVAPosthoc test followed by Dunnet t test.

Table-5: Comparison of mean BAEP wave latencies (ms) of right ear in different menstrual cycle phases

BAEP waves Latencies (ms)	Phase-1 (Mean±SD)	Phase-2 (Mean±SD)	Phase-3 (Mean±SD)
Wave-I	1.67±0.05	1.66±0.12	1.68±0.13
Wave-II	2.78±0.12	2.78±0.07	2.79±0.13
Wave-III	3.65±0.09	3.64±0.14	3.66±0.09
Wave-IV	5.00±0.17	4.99±0.34	5.11±0.38
Wave-V	5.73±0.36	5.51±0.31	5.92±0.52*

(*P<0.05 significant compared Phase-2 with Phase-3 at wave-V)

Table-6: Comparison of mean BAEP wave latencies (ms) of left ear in different menstrual cycle phases

BAEP waves Latencies (ms)	Phase-1 (Mean±SD)	Phase-2 (Mean±SD)	Phase-3 (Mean±SD)
Wave-I	1.68±0.04	1.66±0.11	1.68±0.08
Wave-II	2.79±0.11	2.77±0.07	2.79±0.13
Wave-III	3.65±0.09	3.64±0.13	3.66±0.09
Wave-IV	5.00±0.16	4.99±0.34	5.11±0.38
Wave-V	5.72±0.36	5.52±0.32	5.91±0.43*

(*P<0.05 significant compared Phase-2 with Phase-3 at wave-V)

Fig.5: Comparison of mean BAEP wave latencies (ms) of right ear in different phases of menstrual cycle

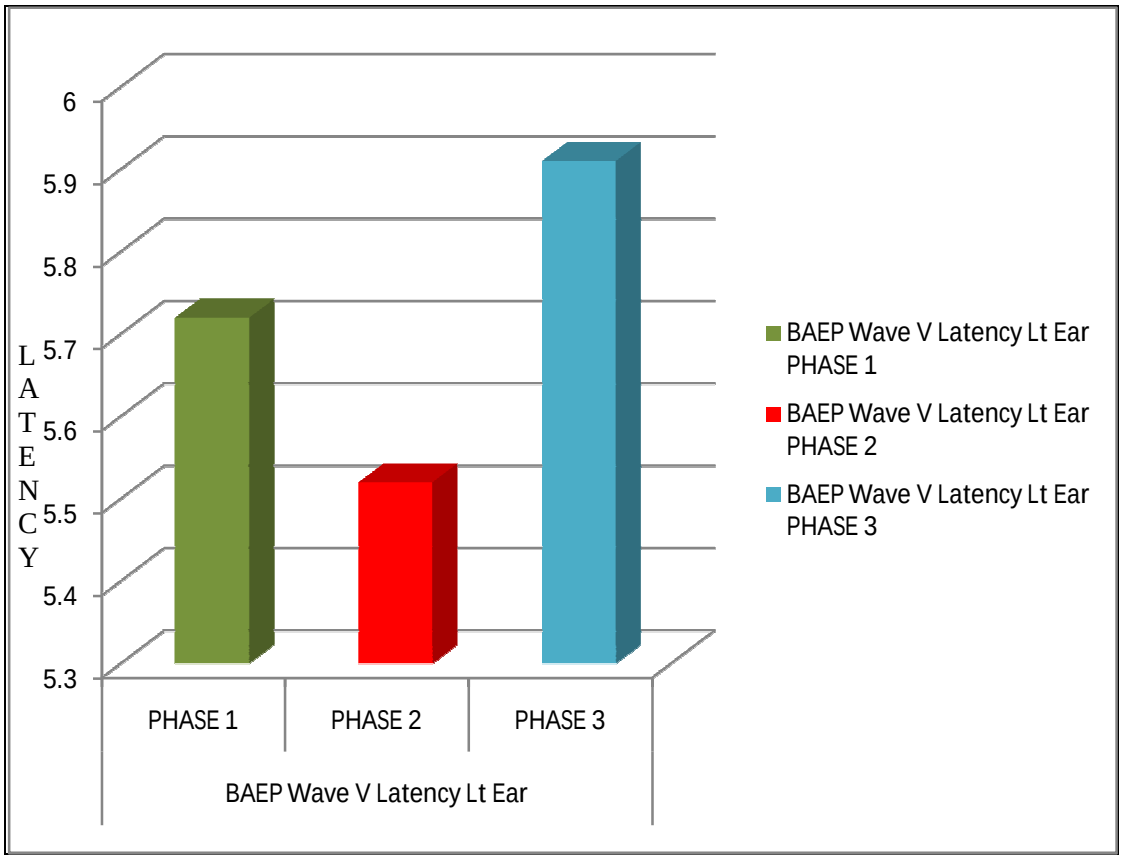


Fig. 6: Comparison of mean BAEP wave latencies (ms) of left ear in different phases of menstrual cycle

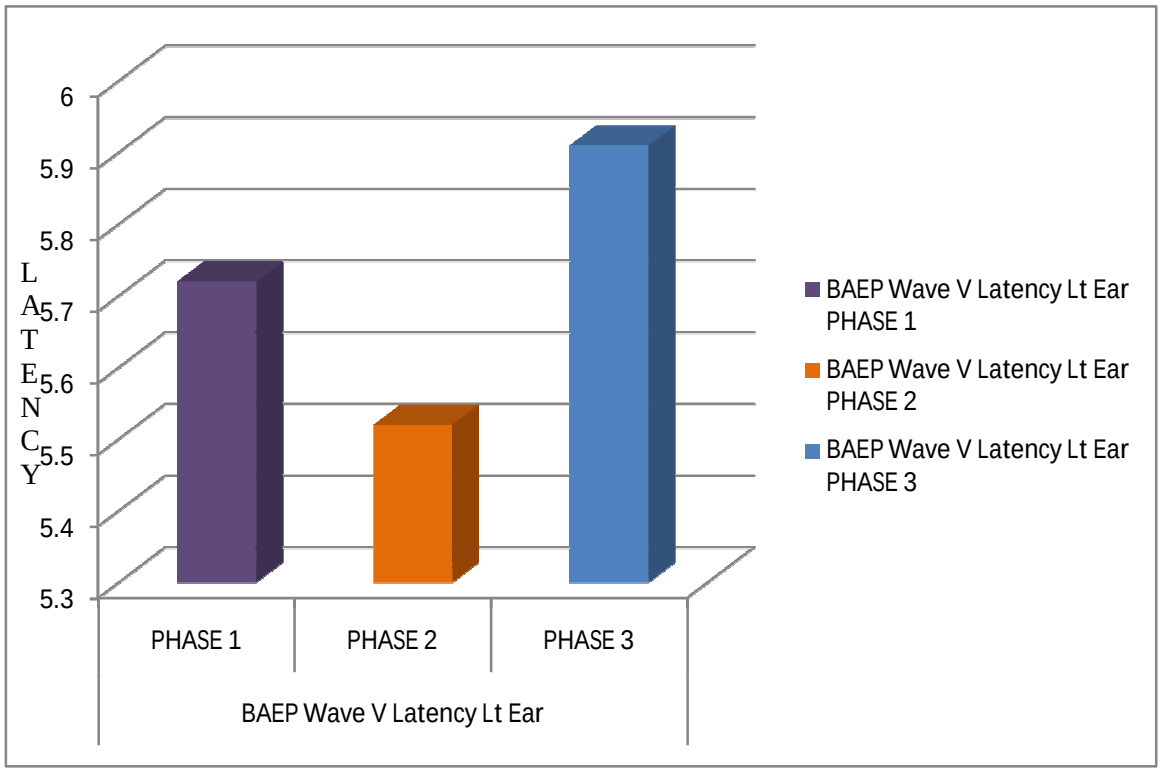


Table-7: Comparison of mean BAEP wave latencies (ms) of left and right ear in different menstrual cycle phases

BAEP waves Phase-1	**Wave-I**	**Wave-II**	**Wave-III**	**Wave-IV**	**Wave-V**
Right ear	1.67±0.05	2.78±0.12	3.65±0.09	5.00±0.17	5.73±0.36
Left ear	1.68±0.04	2.79±0.11	3.65±0.09	5.00±0.16	5.72±0.36
BAEP waves Phase-2	**Wave-I**	**Wave-II**	**Wave-III**	**Wave-IV**	**Wave-V**
Right ear	1.66±0.12	2.78±0.07	3.64±0.14	4.99±0.34	5.51±0.31
Left ear	1.66±0.11	2.77±0.07	3.64±0.13	4.99±0.34	5.52±0.32
BAEP waves Phase-3	**Wave-I**	**Wave-II**	**Wave-III**	**Wave-IV**	**Wave-V**
Right ear	1.68±0.13	2.79±0.13	3.66±0.09	5.11±0.38	5.92±0.52
Left ear	1.68±0.08	2.79±0.13	3.66±0.09	5.70±0.38	5.91±0.43

(P>0.05 no significant difference compared right and left ear waves in different phases)

6.3. Assessment of Inter-peak latency changes in BAEP:

The study showed statistical significant decrease in inter-peak latencies III-V and I-V of Auditory evoked potential on the right side ($p < 0.05$) and also in the left side ($p < 0.05$) during proliferative phase (phase 2) as compared to secretory phase (phase 3) and a statistical significant increase of the same inter-peak latencies during secretory phase (phase 3) as compared to menstrual phase (phase 1) .The inter -peak latency I-III showed the same trend but statistically insignificant. There is no significant difference in the inter-peak latency changes of BAEP on the right side when compared to the left side ($p > 0.05$). The inter-peak latency changes during different phases have been depicted in the table 8, 9 and 10.

Table-8: Comparison of mean inter peak latencies (ms) of right ear in different phases of menstrual cycle

Inter peak latencies (ms)	**Phase-1** (Mean±SD)	**Phase-2** (Mean±SD)	**Phase-3** (Mean±SD)
Wave latency (I-III)	1.99±0.25	1.98±0.23	2.01±0.35
Wave latency (III-V)	2.08±0.26	2.01±0.35	2.13±0.31*
Wave latency (I-V)	4.04±0.30	3.99±0.46	4.14±0.33*

(*P<0.05 significant compared Phase-2with Phase-3 at inter peak-latencies (III-V) and (I-V))

Table-9: Comparison of mean inter peak latencies (ms) of left ear in different phases of menstrual cycle

Inter peak latencies (ms)	**Phase-1** (Mean±SD)	**Phase-2** (Mean±SD)	**Phase-3** (Mean±SD)
Wave latency (I-III)	1.99±0.25	1.99±0.23	2.00±0.34
Wave latency (III-V)	2.09±0.26	2.02±0.35	2.14±0.30*
Wave latency (I-V)	4.04±0.30	3.98±0.46	4.15±0.33*

(*P<0.05 significant compared Phase-2 with Phase-3 at inter peak latencies at (III-V) and (I-V).

Table-10: Comparison of mean inter peak latencies (ms) between right and left ear in different phases of menstrual cycle

Inter peak latencies (ms) Phase-1	**I-III** (Mean±SD**)**	**III-V** **(**Mean±SD**)**	**I-V** (Mean±SD)
Right ear	1.99±0.25	2.08±0.26	4.04±0.30
Left ear	1.99±0.25	2.09±0.26	4.04±0.30
Inter peak latencies (ms) Phase-2	**I-III** (Mean±SD)	**III-V** (Mean±SD)	**I-V** (Mean±SD)
Right ear	1.98±0.23	2.01±0.35	3.99±0.46
Left ear	1.99±0.23	2.02±0.35	3.98±0.46
Inter peak latencies (ms) Phase-3	**I-III** (Mean±SD)	**III-V** (Mean±SD)	**I-V** (Mean±SD)
Right ear	2.01±0.35	2.13±0.31	4.14±0.33
Left ear	2.00±0.34	2.14±0.30	4.15±0.33

(P>0.05 no significant difference compared between right and left ear inter peak latencies at different phases)

6.4. Assessment of amplitude ratio changes in BAEP:

The study showed statistical insignificant decrease in amplitude ratio of BAEP on the right side ($p > 0.05$) and also in the left side ($p > 0.05$) during secretary phase (phase 3) as compared to proliferative phase (phase 2). Also showed a statistically insignificant increase in the same during proliferative phase (phase 2) as compared to menstrual phase (phase 1). There is no significant difference in the amplitude ratio of BAEP on the right side when compared to the left side ($p > 0.05$). The amplitude changes in different phases have been depicted in the table 11 and 12.

Table-11: Comparison of mean V/I wave amplitude ratio of BAEP in right and left ear in different phases of menstrual cycle

Menstrual cycle phase	**Right ear** (Mean±SD)	**Left ear** (Mean±SD)
Phase-1	0.92±0.38	0.93±0.38
Phase-2	1.01±0.40	1.02±0.39
Phase-3	0.90±0.43	0.90±0.42

(P>0.05 no significant difference compared wave amplitude ratio between the different phases)

Table-12: Comparison of mean V/I wave amplitude ratio of BAEP between right and left ear in different phases of menstrual cycle

Ear	Phase-1	Phase-2	Phase-3
Right ear (Mean±SD)	0.92±0.38	1.01±0.40	0.90±0.43
Left ear (Mean±SD)	0.93±0.38	1.02±0.39	0.90±0.42

(P>0.05 no significant difference compared wave amplitude ratio between right and left ear at different phases)

6.5.Assessment of latency changes in VEP:

The study showed statistical significant decrease in wave P100 latency of visual evoked potential on the right side ($p < 0.05$) and also in the left side ($p < 0.05$) during proliferative phase (phase 2) of menstrual cycle as compared to secretory phase (phase 3) and an increase in latency of the same wave during secretory phase (phase 3) as compared to menstrual phase (phase 1).There is no significant difference in the latency changes of VEP on the right side when compared to the left side ($p > 0.05$). The latency changes among the study group have been depicted in the table 13 and 14.

VEP: Visual Evoked Potential

Number of subjects: 80 in each phase

Phase -1: Menstrual phase

Phase -2: Proliferative phase

Phase -3: Secretory phase

Table-13: Comparison of mean VEP wave P100 latency (ms) of right and left eye in different phases of menstrual cycle

Menstrual cycle phase	**Right eye** (Mean±SD)	**Left eye** (Mean±SD)
Phase-1	96.91±0.28	96.90±0.33
Phase-2	95.26±1.08	95.19±1.29
Phase-3	98.10±1.41*	98.00±1.47*

(*P<0.05 significant compared Phase-2 with Phase-3)

Table-14: Comparison of mean VEP wave P100 latency (ms) between right and left eye in different phases of menstrual cycle

Eye	**Phase-1**	**Phase-2**	**Phase-3**
Right eye (Mean±SD)	96.91±0.28	95.26±1.08	98.10±1.41
Left eye (Mean±SD)	96.90±0.33	95.19±1.29	98.00±1.47

(P>0.05 no significant compared between the right and left eye in different phases)

Fig.7: Comparison of mean VEP wave P100 latency (ms) of right eye in different phases of menstrual cycle

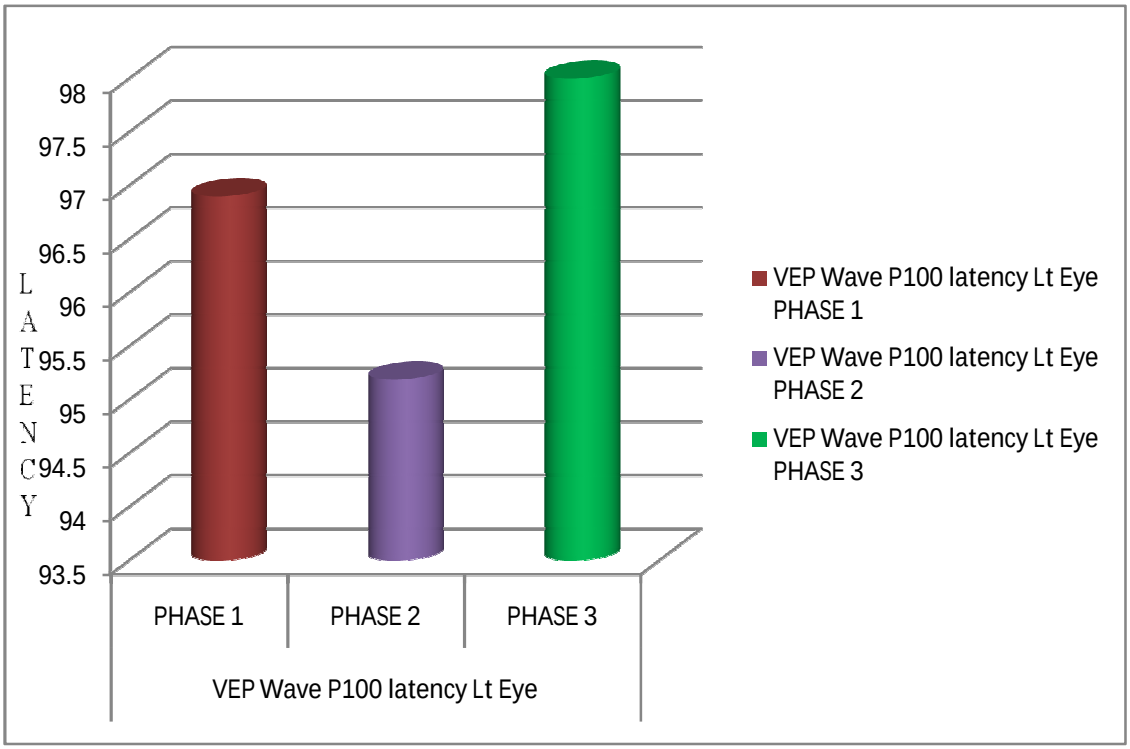
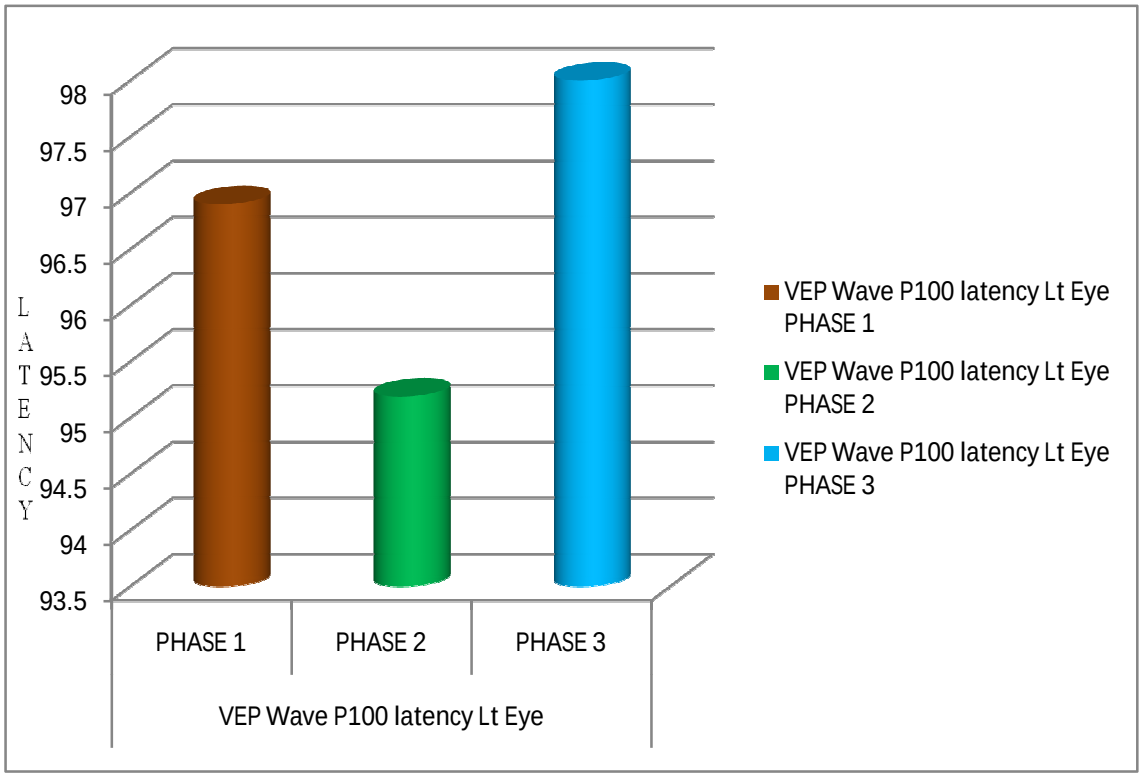


Fig.8: Comparison of mean VEP wave P100 latency (ms) of left eye in different phases of menstrual cycle



6.6.Assessment of amplitude changes in VEP:

The study showed statistical insignificant decrease in amplitude of visual evoked potential wave P100 on the right side (p >0.05) and also in the left side (p >0.05) during secretory phase (phase 3) as compared to proliferative phase (phase 2).Also showed a statistically insignificant increase in the same during proliferative phase (phase 2) as compared to menstrual phase (phase 1). There is no significant difference in the amplitude ratio of VEP on the right side when compared to the left side (p >0.05). The amplitude changes in different phases have been depicted in the table 15 and 16.

Table-15: Comparison of mean P100 wave amplitude of VEP in right and left eye in different phases of menstrual cycle

Menstrual cycle phase	**Right eye** (Mean±SD)	**Left eye** (Mean±SD)
Phase-1	7.82±0.59	7.81±0.59
Phase-2	7.93±0.93	7.94±0.92
Phase-3	7.72±0.79	7.73±0.79

(P>0.05 no significant difference compared wave amplitude between the different phases)

Table-16: Comparison of mean P100 wave amplitudes of VEP between right and left eye in different phases of menstrual cycle

Eye	Phase-1	Phase-2	Phase-3
Right eye (Mean±SD)	7.82±0.59	7.93±0.93	7.72±0.79
Left eye (Mean±SD)	7.81±0.59	7.94±0.92	7.73±0.79

(P>0.05 no significant difference in wave amplitude between right and left eye in different phases)

Data are represented as Mean ± SD

VEP: Visual Evoked Potential

Number of subjects: 80 in each phase

Phase -1: Menstrual phase

Phase -3: Secretory phase

Phase -2: Proliferative phase

DISCUSSION

7. DISCUSSION

The present study is aimed to find out the auditory and visual evoked potential in young healthy females during different phases of menstrual cycle. The menstrual cycle is a time of many widespread changes affecting both body and mind.[40,57]The menstrual cycle influences different clinical conditions such as asthma, atopic dermatitis, diabetes, rheumatoid arthritis**,** pulmonary edema, gastrointestinal dysfunctions & cardiac arrhythmias .[13,58,59] Neurological illnesses such as myasthenia gravis, multiple sclerosis, meningioma, epilepsy, arteriovenous aneurysms, and migraine may be worse during the pre-menstrual phases.[13] EEG also shows variations during different menstrual cycle phases.[13,60]

The hormonal status of a female undergo quantitative changes during menstrual cycle, pregnancy and menopause.[40]Behavioural and neurological symptoms like decreased concentration, nervousness, irritability, emotional instability, poor judgement, tension and depression are seen in women during premenstrual phase.[61,62] This may be due to the effect of gonadal hormones on neural functions.[61]

Recent studies revealed that the estrogen and progesterone have wide spread effects all over the central nervous system including sensory information processing in the brain.[50] Various studies have shown that female sex hormones modulate the threshold, latency and amplitude of auditory, visual and taste sensations.[61]

Evoked potential studies are non-invasive method to assess in real time the processing of sensory information in the human central as well as peripheral nervous system.[28,63] These are electrical signals produced in response to sensory stimuli which

are generated by the nervous system.[64]The evoked potential traces consist of a succession of waves or peaks, which reflect the neuronal responses at the different levels of the sensory pathways.[28] By this technique we can assess the conduction times of the sensory impulses in the CNS.[52]

Brainstem auditory evoked potentials (BAEPs) are electrical potentials generated in response of auditory nerve, brainstem and higher subcortical structures to acoustic stimulus[56] and visual evoked potentials (VEPs) are the cerebral electrical potentials generated by the visual cortex evoked in response to visual stimulus.[51] Therefore, BAEPs and VEPs can be used both in research and in clinical practice toelucidate the function of the auditory and visual system .[52]

Since the hormonal variation during menstrual cycle affect the sensory information processing in peripheral and central auditory and visual pathways, this study is aimed to find the effect of variation in hormones on the peripheral and central conduction time of auditory and visual stimuli. [63]

This study included 80 first year female nursing students of SreeMookambika Institute of Medical Sciences and Research Centre, Kulasekharam. This cross sectional study was conducted in normal healthy female subjects of age 18-25 years who are having regular menstrual cycle and without hearing or visual problems. The ovarian hormones varies during different menstrual cycle phases that is, follicular phase with high level of oestrogen, luteal phase with high level of progesterone and menstrual phase with no influence of hormones.[54, 61] So to find out the variation in

auditory and visual neural conduction in different menstrual cycle phases each subject was subjected to three BAEP and VEP testing within a month time.

The present study showed a decrease in wave latencies and inter-peak latencies during follicular phase with a statistically significant decrease in latency of wave V and inter-peak latencies I-V and III-V in the oestrogen peak follicular phase and a statistically significant increase in the same parameters of BAEP in progesterone peak secretory phase. Similar results are reported by Caruso et al. and Serra et al. with a decrease in BAEP latencies during the periovulatory phase and they suggested that this may be due to the high estrogen level during this phase. High levels of estrogen can modulate glutamate transmission in brainstem and thereby alter the speed of sensory neurotransmission. This is supported by the findings of Coleman et al. showing a shorter BAEP latencies in estrogen treated young OVX rat and the study done by Sisneros et al. in female midshipman fish which showed that on treatment with estradiol their auditory nerves become more sensitive to male mating calls even during the non-breeding season.[37]

On the other hand this study is contradictory to the findings of Dehan and Jerger and Elkind Hirsch et al. showing longer BAEP latencies during the periovulartory phase. The reason they have given is that the high level of estrogen facilitate GABA inhibition in the auditory midbrain by increasing allopregnalone.[37, 38]

Fagan and Church showed no fluctuation inBAEP latencies during the menstrual cycle.[37]

Estrogen receptors are widely distributed in the central nervous system. Both ERα and ERβ are expressed in the peripheral and central auditory system of mammals. In many species, estrogens modulate physiological and behavioural responses to sensory signals, including auditory stimuli. Fluctuations in auditory perception and in electrophysiological measures of auditory function in menstrual cycle shows the importance of estrogen actions on auditory processing.[65,66]Estrogens modulate sensory processing via interactions with neurotransmitters such as dopamine, gamma aminobutyric acid, glutamate, and serotonin by this way it will affect auditory function at different levels of the CNS.[65]

In the menstrual phase, during which gonadal steroids are at a low level, all the BAEP parameters showed a normal value that is similar to that normally found in males.[42]

The amplitude ratio of BAEP wave V/I showed statistically insignificant increase in follicular phase and a decrease in secretory phase .This result is similar to the BAEP study in different menstrual cycle phases, done by Navpreet Mann et al.[7]Caruso et al., Khaliq et al., and Sator et al also showed an increase in BAEP peak amplitudes in postmenopausal women on hormone replacement therapy.[27]

The peak latencies and inter-peak latencies reflect the conduction time in the auditory pathway. This study showed a decrease in wave latencies and inter-peak latencies at follicular phase reflects a faster auditory neural conduction in the estrogen peak phase and an increase in the same parameters during secretory phase reflects a slower auditory neural conduction in the progesterone peak phase. The amplitude ratio

showed statistically insignificant increase in follicular phase and decrease in secretory phase. This may be due to the excitatory action of estrogen on auditory nerve fibres as well as CNS neurons and progesterone has the opposite effect on the CNS.

Due to the excitatory and protective effects of estrogen in CNS, auditory function is found to be better in females than males and also the auditory system is more sensitive during high levels of estrogen in the circulation. [37] Oestrogen enhances synaptic transmission and improve neural conduction. Studies have shown oestrogen replacement treatment can decrease brainstem auditory evoked potential intervals and certain latencies of the Mid latency response (MLR) in postmenopausal women. [34]A decrease in estrogen and decreased metabolism rates could affect the availability of neurotransmitters at the synapse and hence influence neural conduction time.[42]

Estrogen can decrease the number of synaptic vesicles nearby the presynaptic membrane of certain inhibitory synapses. Estrogen increase neuronal excitability by decreasing the $GABA_B$ receptor-mediated autoinhibition of the GABAergicpreoptic area as well as the ability of those neurons to synthesize GABA. Progesterone potentiates GABA receptor activation by a nongenomic mechanism that may involve actions at the plasma membrane. Progesterone decrease neuronal excitability by formation of allopregnanolone, which is a positive modulator of GABA and it increases inhibitory chloride ion conductance.[67]

In our study there was a statistically significant decrease in wave V latency and inter-peak latencies III-V and I-V during follicular phase and an increase in the same parameters during secretory phase .This may be due to the high influence of ovarian

hormones on higher levels of auditory pathway. Other BAEP waves and inter-peak latency I-III showed statistically insignificant decrease during follicular phase and statistically insignificant increase in the same parameters during secretory phase. This may be indirectly reflects the much less effect of the ovarian hormones on lower levels of auditory pathway.

Some studies which showed similar results like our study. The study done by Caruso et al. showed shorter latencies of BAEP waves and interpeak intervals after 3 months of estrogen therapy when compared to baseline. Guimaraes et al. investigated the auditory system of postmenopausal women who were receiving combined hormone treatment (Estrogen + Progesterone) and compared this group to a group treated only with estrogen (E) and to a control group (CG). The findings shows a protective effect of estradiol on the female auditory system and that the addition of progestin seems to have a negative influence on the peripheral and central auditory system.[37, 38]

Broadly, estrogen seems to have more positive than negative effects to the auditory system. On the other hand, progestin seems to have more negative than positive effect on the auditory system. One possible mechanism for progesterone's negative effects on hearing centers on progesterone's ability to down regulate estrogen receptors in breast and uterine tissue, balancing the effects of estrogen or possible irreversible receptor damage.[38]The estrogen and other gonadal steroids act directly on the receptors upon the cochlea and various central auditory system pathways. Through other pathways they could indirectly influence central processing and also

regulate blood flow as well as fluid electrolyte balance in the cochlea. They modulate the effects of neurotransmitters present along the auditory pathways.[37, 42]

Estrogen has been found by some investigators as neuroprotective, and vasoprotective, as it is thought to produce favourable effects in axonal sprouting, regenerative responses, enhanced synaptic transmission and enhanced neurogenesis. Further its effects in direct modulation of neurotransmitter receptor functions, and antioxidant activities have been attributed for decrease in latency of BAEP in estrogenic phase.[37, 68]Estrogens are important in the development, maintenance and physiology of the CNS.[14]

The visual evoked potential is defined as the electrical response arise from the neurons in visual cortex which is evoked by visual stimulation.[51] This study showed a statistically significant decrease in latency of VEP wave P100 in the oestrogen peak follicular phase and a statistically significant increase in the same in progesterone peak secretory phase. This may be due to facilitating effect of estrogen on the visual neural conduction.[55, 68] Various studies reported that estrogen cause a decrease in the visual transmission time by increasing the sensitivity of receptors in the optic pathways to dopamine. [50, 68]Estrogen augments glutamate effects by binding to receptors that are widely present in the CNS and cause excitatory effects in the cell level. In addition, estrogen inhibit glutamate decarboxylase (GAD) enzyme and thereby the synthesis of GABA, via the widely distributed receptors in the CNS. When GABA synthesis is inhibited, excitatory effects become prominent and changes in VEP morphology and decrease in latency occurs.[68]From animal experiments it has been proven that progesterone metabolites enhance the action of gamma-

aminobutyricacid (GABA) the main inhibitory neurotransmitter in the cortex, producing benzodiazepine-like physiologic and behavioral effects. Estradiol has excitatory effects on measures of neuronal excitability, possibly acting through the glutamate system.[69]

Prolongation of VEP latency during the secretory phase of menstrual cycle probably reflects the effect of progesterone.[54] There was prolongation of P100 latency during secretory phase also seen in studies done before by Kaned Y as well as Mohsen Azarmina MD and few more.[53, 54, 68] Increased latency of P100 is supporting the view that there is effect of progesterone on neuronal conductivity. The most probable reasons for increased VEP latency during secretory phase may be the decrease in blood estrogen levels and diminution of the neuroprotective effect of estrogen and the vascular congestion around the optic nerve reducing conduction velocity.[54]

The amplitude of VEP wave P100 showed statistically insignificant increase in follicular phase and a decrease in secretory phase.HikmetYilmaz et al. showed a similar result in VEP amplitude during menstrual cycle. [68]VEP amplitude has been shown to be increased by estrogen directly and/or indirectly through L-type voltage-dependent calcium channels, acetylcholine, monoamines, γ-aminobutyric acid or glutamate, and to be inhibited by progesterone directly and/or indirectly through γ-aminobutyric acid or glutamate.[12, 53]

The VEP parameters showed a normal value in menstrual phase, during which ovarian hormones are at a minimum level .This value is seems to be similar to that normally found in males.[42]

VEPs have emerged as an important diagnostic tool in demyelinating diseases of the central nervous system in the current era. The clinical implication of these findings is in the application of VEP for confirming demyelinative disease and optic neuritis. In such cases one should take into account that prolongation of VEP latency during menstruation may erroneously verify demylinating disease.

From the present study it has been found that the sensory neural conduction through the auditory and optic nerve is faster during estrogen peaked proliferative phase and slower during progesterone peaked secretory phase. This may be due to the neuronal excitatory action of the sex steroid estrogen causing a decrease in auditory and visual neural conduction time during proliferative phase and an increase in the same during secretory phase due to the inhibitory effect of progesterone.

The study needs to be further elaborated regarding the estimation of the blood levels of oestrogen and progesterone in all the phases. Since the phases of menstrual cycle can affect the result of BAEP and VEP thus at the time of recording menstrual history should be taken properly and patient is in which phase is to be confirmed. Along with this a normative values, for the device used in the institution should be generated with normal healthy subjects of all age groups so possibilities of false reporting can be cut short.

CONCLUSION

8.CONCLUSION

The hearing conduction as measured by Brain Stem Auditory Evoked Potential (BAEP) and visual neural conduction as measured by Visual Evoked Potential (VEP) are better in proliferative phase as compared to secretory phase of menstrual cycle. The menstrual cycle phases affect hearing as well as vision due to variation in levels of ovarian hormones; estrogen is the likely hormone responsible for the faster conduction in the auditory and visual pathways. BAEP wave latencies and inter peak latencies as well as VEP wave latencies have important diagnostic values. The interpretative accuracy of the evaluation of the BAEPs and VEPs can be enhanced only when these normal variations are taken into consideration with relevant case history information.

This study showed that normal cyclical variation in gonadal hormones especially estrogen and progesterone modifies the central processing of the auditory and visual information.

SUMMARY

9. SUMMARY

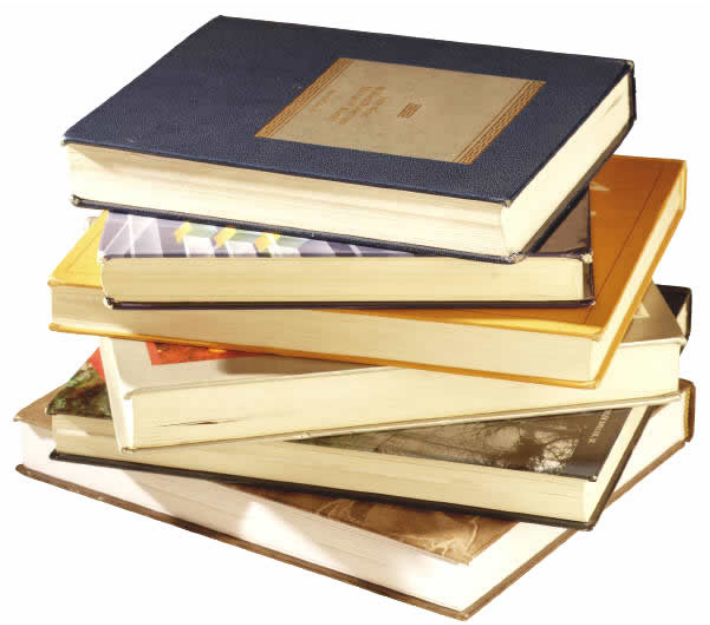
The menstrual cycle is a normal phenomenon that takes place during the reproductive period of a female. This is manifested by monthly discharge of blood from the female genital tract. The hormonal variations that occur during the menstrual cycle affect not only the reproductive tract but also overall the body including CNS. These changes in CNS especially in sensory system can be detected with the help of evoked potential studies.

Hearing and vision are the most important among the sensory modalities, so this study is aimed to find the differences in auditory and visual neural conduction time in different phases of menstrual cycle. There occurs a wide variation in gonadal hormones during the different phases of menstrual cycle this will affect the auditory and visual neural conduction throughout the cycle.

Brainstem Auditory Evoked Potential (BAEP) is an objective, low cost and non-invasive method of hearing assessment which detects electrical activity from the inner ear to the inferior colliculus.[31]Visual evoked potentials are the record of electrophysiological potential response originating from the occipital cortex by retinal stimulation.[49] By this we can assess the functional integrity of the visual system.[12]

This cross sectional study was conducted in 80 female nursing students with regular menstrual cycle. After getting the informed consent all subjects were subjected to three Brainstem Auditory Evoked Potential (BAEP) testing and Visual Evoked Potential (VEP) testing during three phases of their menstrual cycle namely menstrual (phase 1), proliferative (phase 2), and secretory (phase 3).

From the present study, it is evident that the absolute latencies of all the waves of the BAEP and VEP as well as the inter-peak latencies of BAEP waves showed a decrease in the proliferative phase and hence, this enhanced the conduction across the neural pathways. On the other hand, the absolute latencies of the various BAEP and VEP waves as well as the inter-peak latencies of BAEP waves in the secretory phase were increased, which showed a slower neural conduction. The VEP amplitude and BAEP amplitude ratio showed an increase in proliferative phase as compared to secretory phase. This can be due to the excitatory and neuroprotective effect of oestrogen in the proliferative phase, and the antagonistic effect of progesterone in the secretory phase.



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ANNEXURES

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161

Phone No: 04651-280866, Fax No. 04651-280740

Institutional Human Ethics Committee

Registered under CDSCO with Reg No. ECR/446/Inst/TN/2013

Ref. No. SMIMS/IHEC/2013/C/06 **Date: 27th December 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/C/06,** entitled "A Study on Auditory and Visual Evoked Potential in Young Healthy Females During Different Phases of Menstrual Cycle" submitted by Dr. Lisha Vincent, Postgraduate of Department of Physiology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 19th of December 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES
IHEC
Date 27/12/2013
KULASEKHARAM

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam [K.K District]
Tamil Nadu -629161

CONSENT FORM

PART II

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled 'A study on Auditory and Visual evoked potential in young healthy females during different phases of menstrual cycle.'

Serial No/Reference No :

Name of the participant : **Address of the participant:**

Contact Number of the participant:

Signature/Thumb impression of the participant/Legal guardian.

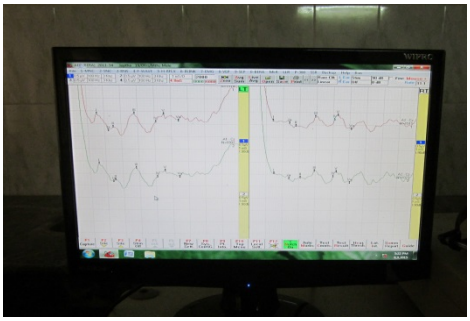
Witness:

1.

2.

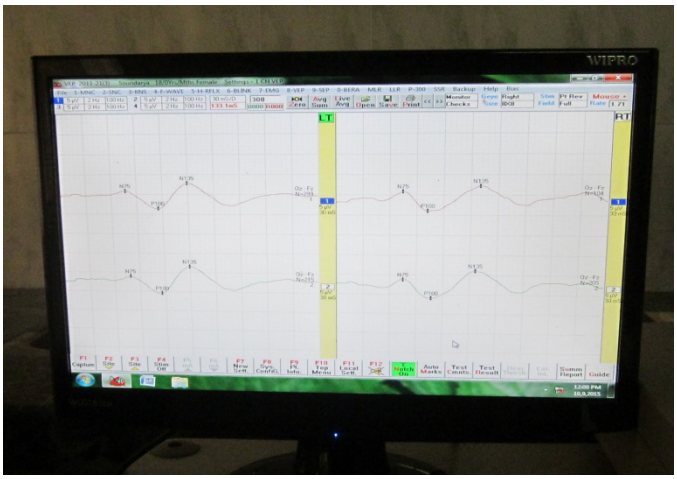
Date:

Place:IMAGE 1: COMPUTERIZED RMS ALERON 401 EMG/NCV/EP SYSTEM



BAEP WAVES

IMAGE 2: COMPUTERIZED RMS ALERON 401 EMG/NCV/EP SYSTEM



VEP WAVES

11.5. ABBREVIATIONS:

ABR	:	Auditory Brainstem Response
AEPs	:	Auditory Evoked Potentials
AVCN	:	Anterior Ventral Cochlear Nucleus
ANOVA	:	Analysis Of Variance
BAEP	:	Brainstem Auditory Evoked Potential
BBT	:	Basal Body Temperature
BSERs	:	Brainstem Evoked Responses
CNS	:	Central Nervous System
DCN	:	Dorsal Cochlear Nucleus
EP	:	Evoked Potential
ER	:	Estrogen Receptor
FSH	:	Follicle Stimulating Hormone
GBG	:	Gonadal Steroid Binding Globulin
GnRH	:	Gonadotrophin Releasing Hormone
IHEC	:	Institutional Human Ethical Committee
IPLs	:	Inter peak Latencies
LH	:	Leutinizing Hormone
mm	:	Millimeter
m-RNA	:	Messenger RNA
msec	:	Millisecond
mV	:	Millivolt
PSVEP	:	Pattern Shift Visual Evoked Potential
PVCN	:	Posterior Ventral Cochlear Nucleus
SD	:	Standard Deviation
VEP	:	Visual Evoked Potential

Brainstem Auditory Evoked Potential(BAEP)												
WAVE-I latency							**WAVE-II latency**					
Right Ear				**Left Ear**			**Right Ear**			**Left Ear**		
Sl.No	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**
1	1.69	1.8	1.79	1.68	1.4	1.74	2.6	2.79	2.77	2.66	2.72	2.87
2	1.65	1.7	1.77	1.69	1.64	1.78	2.8	2.5	2.89	2.78	2.76	2.85
3	1.61	1.65	1.74	1.69	1.48	1.68	2.68	2.76	2.78	2.52	2.81	2.97
4	1.65	1.67	1.71	1.6	1.68	1.67	2.77	2.74	2.85	2.7	2.79	2.88
5	1.69	1.78	1.77	1.69	1.64	1.64	2.73	2.72	2.76	2.89	2.89	2.56
6	1.69	1.69	1.75	1.69	1.63	1.68	2.76	2.76	2.78	2.52	2.76	2.76
7	1.68	1.77	1.8	1.64	1.6	1.65	2.77	2.79	2.89	2.59	2.86	2.57
8	1.67	1.64	1.78	1.68	1.65	1.63	2.86	2.8	2.82	2.67	2.75	2.76
9	1.68	1.6	1.48	1.69	1.38	1.38	2.97	2.89	2.78	2.74	2.85	2.5
10	1.69	1.62	1.79	1.66	1.7	1.76	2.79	2.76	2.86	2.52	2.76	2.6
11	1.6	1.3	1.34	1.69	1.63	1.73	2.64	2.8	2.85	2.86	2.81	2.5
12	1.69	1.66	1.78	1.69	1.67	1.74	2.78	2.75	2.81	2.6	2.79	2.5
13	1.62	1.44	1.45	1.6	1.64	1.7	2.79	2.78	2.79	2.85	2.67	2.65
14	1.64	1.71	1.75	1.69	1.69	1.72	2.8	2.75	2.86	2.78	2.74	2.94

15	1.69	1.64	1.47	1.64	1.64	1.74	2.85	2.81	2.85	2.73	2.71	2.56
16	1.68	1.7	1.79	1.72	1.83	1.76	2.59	2.86	2.76	2.78	2.89	2.74
17	1.69	1.7	1.73	1.69	1.64	1.7	2.73	2.74	2.88	2.8	2.7	2.78
18	1.63	1.44	1.74	1.69	1.63	1.74	2.78	2.74	2.87	2.78	2.8	2.56
19	1.73	1.78	1.38	1.6	1.62	1.71	2.79	2.71	2.86	2.68	2.73	2.69
20	1.69	1.65	1.75	1.69	1.75	1.79	2.8	2.89	2.87	2.78	2.85	2.52
21	1.62	1.68	1.73	1.66	1.63	1.7	2.79	2.8	2.78	2.68	2.73	2.73
22	1.69	1.67	1.76	1.7	1.39	1.72	2.86	2.7	2.87	2.75	2.77	2.73
23	1.68	1.66	1.47	1.7	1.74	1.72	2.79	2.88	2.88	2.98	2.7	2.88
24	1.61	1.75	1.72	1.69	1.67	1.73	2.88	2.86	2.86	2.78	2.87	2.95
25	1.69	1.68	1.74	1.74	1.85	1.76	2.7	2.89	2.79	2.74	2.7	2.88
26	1.63	1.68	1.74	1.69	1.78	1.8	2.75	2.88	2.99	2.88	2.8	2.76
27	1.7	1.85	1.75	1.7	1.71	1.79	2.64	2.75	2.83	2.68	2.77	2.98
28	1.68	1.68	1.49	1.6	1.63	1.79	2.78	2.87	2.84	2.89	2.79	2.78
29	1.67	1.47	1.39	1.7	1.84	1.82	2.88	2.8	2.52	2.87	2.5	2.65
30	1.69	1.6	1.7	1.8	1.81	1.8	2.97	2.88	2.65	2.9	2.76	2.94
31	1.69	1.68	1.77	1.69	1.45	1.7	2.88	2.75	2.66	2.93	2.74	2.96
32	1.69	1.49	1.75	1.8	1.64	1.81	2.79	2.79	2.91	2.98	2.72	2.6
33	1.69	1.66	1.78	1.67	1.84	1.79	2.87	2.78	2.9	2.78	2.8	2.95
34	1.6	1.66	1.71	1.8	1.82	1.72	2.66	2.76	2.87	2.52	2.81	2.94

35	1.61	1.48	1.73	1.69	1.7	1.68	2.9	2.74	2.85	2.9	2.8	2.73
36	1.68	1.4	1.74	1.7	1.63	1.61	2.52	2.72	2.97	2.95	2.7	2.88
37	1.69	1.64	1.48	1.62	1.64	1.63	2.52	2.76	2.88	2.98	2.76	2.87
38	1.69	1.48	1.78	1.73	1.8	1.64	2.89	2.81	2.56	2.96	2.8	2.73
39	1.69	1.68	1.77	1.63	1.69	1.64	2.52	2.79	2.76	2.97	2.8	2.8
40	1.69	1.64	1.44	1.8	1.82	1.7	2.59	2.89	2.57	2.8	2.85	2.76
41	1.69	1.63	1.78	1.61	1.63	1.63	2.67	2.76	2.76	2.79	2.77	2.88
42	1.75	1.6	1.45	1.63	1.6	1.64	2.74	2.86	2.5	2.78	2.81	2.66
43	1.68	1.65	1.73	1.6	1.8	1.6	2.52	2.75	2.6	2.88	2.8	2.68
44	1.69	1.38	1.38	1.7	1.84	1.8	2.9	2.85	2.5	2.85	2.8	2.96
45	1.66	1.7	1.76	1.64	1.68	1.67	2.6	2.76	2.5	2.9	2.74	2.86
46	1.69	1.63	1.43	1.69	1.8	1.69	2.85	2.81	2.65	2.73	2.79	2.84
47	1.69	1.67	1.74	1.65	1.7	1.67	2.79	2.79	2.94	2.78	2.5	2.89
48	1.6	1.64	1.7	1.61	1.65	1.64	2.73	2.67	2.56	2.6	2.76	2.77
49	1.69	1.69	1.42	1.69	1.67	1.61	2.79	2.74	2.74	2.8	2.74	2.89
50	1.64	1.64	1.74	1.69	1.78	1.67	2.8	2.71	2.78	2.68	2.72	2.78
51	1.72	1.83	1.76	1.69	1.69	1.65	2.97	2.89	2.56	2.77	2.76	2.85
52	1.69	1.64	1.7	1.68	1.77	1.8	2.68	2.7	2.69	2.73	2.79	2.76
53	1.69	1.63	1.44	1.7	1.64	1.78	2.78	2.8	2.52	2.76	2.8	2.78
54	1.69	1.62	1.71	1.68	1.6	1.78	2.68	2.73	2.73	2.77	2.89	2.89

55	1.69	1.75	1.49	1.69	1.62	1.69	2.75	2.85	2.73	2.86	2.76	2.82
56	1.7	1.63	1.7	1.69	1.3	1.34	2.98	2.73	3.02	2.97	2.8	2.78
57	1.7	1.39	1.42	1.69	1.66	1.68	2.78	2.77	2.95	2.79	2.75	2.86
58	1.7	1.74	1.72	1.73	1.44	1.65	2.74	2.7	2.88	2.64	2.78	2.85
59	1.69	1.67	1.73	1.64	1.71	1.65	2.88	2.87	2.76	2.95	2.75	2.81
60	1.74	1.85	1.76	1.69	1.64	1.67	2.68	2.7	2.8	2.97	2.81	2.79
61	1.69	1.78	1.8	1.68	1.7	1.69	2.89	2.8	2.78	2.8	2.86	2.86
62	1.7	1.71	1.79	1.69	1.7	1.63	2.87	2.77	2.79	2.85	2.74	2.85
63	1.6	1.63	1.79	1.63	1.44	1.64	2.9	2.79	2.94	2.59	2.74	2.94
64	1.75	1.84	1.82	1.73	1.78	1.69	2.93	2.5	2.96	2.73	2.71	2.88
65	1.8	1.81	1.8	1.69	1.65	1.65	2.98	2.76	2.9	2.78	2.89	2.87
66	1.69	1.45	1.7	1.62	1.68	1.63	2.78	2.74	2.95	2.79	2.8	2.86
67	1.8	1.64	1.81	1.68	1.67	1.66	2.52	2.72	2.94	2.8	2.7	2.87
68	1.78	1.84	1.79	1.7	1.66	1.67	2.9	2.8	2.73	2.79	2.88	2.97
69	1.8	1.82	1.82	1.61	1.75	1.62	2.95	2.81	2.88	2.86	2.86	2.87
70	1.69	1.7	1.78	1.68	1.68	1.64	2.79	2.8	2.87	2.79	2.78	2.88
71	1.7	1.63	1.71	1.63	1.68	1.64	2.96	2.7	2.73	2.88	2.88	2.86
72	1.62	1.64	1.73	1.7	1.85	1.65	2.97	2.76	2.78	2.87	2.75	2.8
73	1.73	1.8	1.74	1.68	1.68	1.69	2.8	2.8	2.76	2.75	2.87	2.8
74	1.63	1.69	1.74	1.67	1.67	1.67	2.77	2.8	2.88	2.64	2.8	2.83

75	1.8	1.82	1.81	1.69	1.6	1.6	2.78	2.85	2.66	2.76	2.7	2.84
76	1.61	1.63	1.73	1.69	1.68	1.67	2.88	2.77	2.68	2.88	2.75	2.6
77	1.63	1.6	1.74	1.69	1.49	1.65	2.85	2.81	2.96	2.79	2.79	2.65
78	1.6	1.8	1.7	1.69	1.66	1.68	2.9	2.8	2.86	2.79	2.78	2.66
79	1.6	1.84	1.8	1.6	1.66	1.61	2.73	2.8	2.84	2.79	2.76	2.91
80	1.64	1.68	1.77	1.7	1.48	1.63	2.78	2.74	2.89	2.87	2.74	2.9

Brainstem Auditory Evoked Potential(BAEP)												
WAVE-III latency							WAVE-IV latency					
Right Ear				Left Ear			Right Ear			Left Ear		
Sl.No	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3
1	3.54	3.5	3.69	3.94	3.67	3.52	5.2	4.52	4.62	5.08	4.98	5.06
2	3.75	3.5	3.54	3.74	3.66	3.35	5.08	5.06	4.98	5.06	4.97	4.99
3	3.5	3.59	3.69	3.69	3.94	3.72	5.32	5.2	4.94	4.77	4.98	4.77
4	3.5	3.55	3.67	3.63	3.55	3.74	4.98	5.08	5.2	5.08	4.94	4.73
5	3.94	3.57	3.63	3.55	3.57	3.67	5.2	5.08	5.79	5.02	5.08	5.08
6	3.68	3.65	3.67	3.71	3.56	3.67	5.22	5.23	5.76	5	5.08	5.08
7	3.66	3.56	3.68	3.72	3.57	3.7	4.94	4.87	5.65	4.94	5.06	5.08
8	3.63	3.94	3.66	3.67	3.94	3.74	5.08	4.98	5.88	4.88	4.98	5.2
9	3.55	3.57	3.72	3.55	3.7	3.74	5.06	4.94	5.73	4.52	4.6	4.81
10	3.71	3.59	3.67	3.56	3.55	3.71	5.34	5.08	5.68	5.06	4.73	4.77
11	3.72	3.59	3.72	3.65	3.59	3.35	5.08	5.08	5.75	4.9	4.08	5.32

12	3.67	3.57	3.74	3.55	3.51	3.71	5.02	5.06	5.08	5.08	4.08	4.94
13	3.68	3.68	3.68	3.65	3.57	3.65	5.1	4.99	5.95	4.56	4.08	4.83
14	3.66	3.7	3.69	3.69	3.69	3.74	4.94	4.77	5.81	4.94	4.99	4.77
15	3.73	3.55	3.68	3.64	3.72	3.71	5	4.73	5.8	4.81	4.81	5
16	3.66	3.56	3.69	3.75	3.55	3.67	5.12	5.08	5.73	4.81	4.87	4.85
17	3.65	3.51	3.67	3.66	3.54	3.5	5.06	5.08	5.95	5.06	4.42	5.02
18	3.66	3.56	3.65	3.92	3.5	3.52	4.9	5.08	5.56	4.98	4.94	4.5
19	3.64	3.7	3.74	3.55	3.51	3.7	5.08	4.5	5.77	5.08	5.56	5.06
20	3.75	3.51	3.71	3.67	3.54	3.71	4.99	4.81	5.88	5.3	5.77	4.99
21	3.54	3.55	3.67	3.72	3.94	3.74	4.94	4.77	5.85	4.98	4.98	5.06
22	3.92	3.67	3.68	3.69	3.94	3.67	4.93	5.52	5.02	4.85	4.62	4.87
23	3.55	3.59	3.66	3.68	3.59	3.6	4.81	5.95	5.06	5.02	4.98	5.08
24	3.67	3.7	3.7	3.72	3.55	3.35	5.06	5.83	5.06	5.34	4.94	5.08
25	3.56	3.59	3.71	3.75	3.53	3.74	4.5	5.77	4.52	5.08	5.08	4.98
26	3.58	3.72	3.74	3.66	3.55	3.69	5.08	5	5.06	5.11	4.79	4.97
27	3.56	3.94	3.67	3.65	3.9	3.74	4.8	5.85	5.2	4.78	5.06	4.98
28	3.58	3.69	3.6	3.75	3.66	3.69	4.96	5.02	5.08	5.32	4.97	4.94
29	3.59	3.65	3.66	3.67	3.65	3.58	4.98	5.06	5.08	4.99	5.1	5.08
30	3.65	3.66	3.74	3.5	3.67	3.63	5.02	5.06	4.52	4.77	4.73	5.08
31	3.75	3.65	3.69	3.55	3.65	3.52	4.99	4.52	4.87	5.08	5.08	5.06

32	3.55	3.9	3.74	3.59	3.6	3.35	5.08	5.06	4.98	5.06	4.75	4.98
33	3.75	3.66	3.69	3.69	3.94	3.72	4.9	4.87	4.94	4.77	5.08	5.31
34	3.56	3.65	3.7	3.63	3.58	3.74	5.3	5.08	5.08	5.08	5.3	4.73
35	3.66	3.69	3.63	3.55	3.44	3.67	5.02	5.08	5.08	5.02	5	4.7
36	3.94	3.67	3.52	3.71	3.59	3.67	5.31	4.98	5.06	4.87	5.6	4.5
37	3.74	3.66	3.35	3.57	3.57	3.7	4.77	4.97	4.99	4.94	4.87	4.67
38	3.69	3.94	3.72	3.67	3.94	3.74	5.08	4.98	4.77	4.98	4.94	4.99
39	3.63	3.55	3.74	3.48	3.9	3.74	5.06	4.94	4.73	5.21	5.3	4.81
40	3.55	3.57	3.67	3.5	3.52	3.71	4.77	5.08	5.08	5.06	4.77	4.87
41	3.71	3.56	3.67	3.73	3.44	3.35	5.08	5.08	5.08	4.9	5.11	4.5
42	3.72	3.57	3.7	3.66	3.51	3.71	5.02	5.06	5.08	5.08	4.85	4.94
43	3.67	3.94	3.74	3.55	3.57	3.65	5	4.98	5.2	4.99	5.02	4.9
44	3.55	3.7	3.74	3.68	3.9	3.74	4.94	4.6	4.81	5.2	5.06	4.77
45	3.56	3.55	3.71	3.55	3.59	3.71	4.88	4.73	4.77	5.08	5.06	4.98
46	3.65	3.59	3.35	3.54	3.5	3.69	4.52	4.08	5.32	5.32	4.52	4.62
47	3.55	3.51	3.71	3.75	3.5	3.68	5.06	4.08	4.94	4.98	5.06	4.98
48	3.65	3.57	3.65	3.5	3.59	3.69	4.9	4.08	4.83	5.2	5.2	4.94
49	3.69	3.9	3.74	3.5	3.55	3.67	5.08	4.99	4.77	5.22	5.08	5.2
50	3.64	3.72	3.71	3.94	3.57	3.63	4.56	4.81	5	4.94	5.08	5.79
51	3.75	3.55	3.67	3.68	3.65	3.67	4.94	4.87	4.85	5.08	5.23	5.76

52	3.66	3.54	3.5	3.66	3.56	3.68	4.81	4.42	5.02	5.06	4.87	5.65
53	3.92	3.5	3.52	3.63	3.94	3.66	4.81	4.94	4.5	5.34	4.98	5.88
54	3.55	3.51	3.7	3.55	3.57	3.72	5.06	5.56	5.06	5.08	4.94	5.73
55	3.67	3.54	3.71	3.71	3.59	3.67	4.98	5.77	4.99	5.02	5.08	5.68
56	3.72	3.94	3.74	3.72	3.59	3.72	5.08	4.98	5.06	5.1	5.08	5.75
57	3.69	3.94	3.67	3.67	3.57	3.74	5.3	4.62	4.87	4.94	5.06	5.08
58	3.68	3.59	3.6	3.68	3.68	3.68	4.98	4.98	5.08	5	4.99	5.95
59	3.72	3.55	3.35	3.66	3.7	3.69	4.85	4.94	5.08	5.12	4.77	5.81
60	3.75	3.53	3.74	3.73	3.55	3.7	5.02	5.08	4.98	5.06	4.73	5.8
61	3.66	3.55	3.69	3.66	3.56	3.69	5.34	4.79	4.97	4.9	5.08	5.73
62	3.65	3.9	3.74	3.65	3.51	3.67	5.08	5.06	4.98	5.08	5.08	5.95
63	3.75	3.66	3.69	3.66	3.56	3.65	5.11	4.97	4.94	4.99	5.08	5.56
64	3.67	3.65	3.58	3.64	3.7	3.74	4.78	5.1	5.08	4.94	4.5	5.77
65	3.5	3.67	3.63	3.75	3.51	3.71	5.32	4.73	5.08	4.93	4.81	5.88
66	3.55	3.65	3.52	3.54	3.55	3.67	4.99	5.08	5.06	4.81	4.77	5.85
67	3.59	3.6	3.35	3.92	3.67	3.68	4.77	4.75	4.98	5.06	5.52	5.02
68	3.69	3.94	3.72	3.66	3.59	3.66	5.08	5.08	5.31	4.5	5.95	5.06
69	3.63	3.58	3.74	3.67	3.7	3.7	5.06	5.3	4.73	5.08	5.83	5.06
70	3.55	3.44	3.67	3.56	3.59	3.71	4.77	5	4.7	4.8	5.77	4.52
71	3.71	3.59	3.67	3.58	3.72	3.74	5.08	5.6	4.5	4.96	5	5.06

72	3.57	3.57	3.7	3.67	3.94	3.67	5.02	4.87	4.67	4.98	5.85	5.2
73	3.67	3.94	3.74	3.58	3.69	3.6	4.87	4.94	4.99	5.02	5.02	5.08
74	3.48	3.9	3.74	3.59	3.65	3.66	4.94	5.3	4.81	4.99	5.06	5.08
75	3.5	3.52	3.71	3.65	3.66	3.74	4.98	4.77	4.87	5.08	5.06	4.52
76	3.73	3.44	3.35	3.75	3.65	3.69	5.21	5.11	4.5	5.2	4.52	4.87
77	3.66	3.51	3.71	3.65	3.9	3.74	5.06	4.85	4.94	4.99	5.06	4.98
78	3.55	3.57	3.65	3.75	3.66	3.69	4.9	5.02	4.9	5.02	4.87	4.94
79	3.68	3.9	3.74	3.56	3.65	3.7	5.08	5.06	4.77	5.31	5.08	5.08
80	3.55	3.59	3.71	3.66	3.64	3.63	4.99	5.06	4.98	4.77	5.08	5.08

Brainstem Auditory Evoked Potential(BAEP)												
WAVE-V Latency							INTERPEAK Latency I-III					
Right Ear				Left Ear			Right Ear			Left Ear		
Sl.No	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3
1	6.22	5.4	6.01	6.23	5.44	6.4	1.94	1.96	2.35	1.92	1.96	1.71
2	6.32	5.49	6.15	5.88	5.21	5.97	1.96	1.98	2.08	2.4	1.98	1.96
3	6.21	5.35	6.3	5.4	5.4	6.02	1.83	1.99	1.71	1.74	1.99	2.4
4	6.2	5.42	5.89	5.67	5.23	5.5	1.98	1.48	2.04	2.33	1.48	2.44
5	6.03	5.4	6.35	5.21	5.59	5.87	1.99	1.93	2.35	2.52	1.93	2.48
6	6.012	6	5.95	5.44	5.4	5.88	1.85	1.95	1.35	2.52	1.95	2.08
7	5.98	5.11	6.02	5.27	5.4	6.15	1.68	1.75	2.35	1.85	1.75	2.1
8	5.88	5.69	5	5.31	5.35	6.12	1.97	2.48	2.52	1.83	2.48	2
9	6.06	5.49	6.01	5.4	5.02	6	1.92	1.99	1.65	1.85	1.99	2
10	6.03	5.3	6.22	5.44	5.23	5.78	2.4	1.98	2	1.62	1.98	1.35
11	5.99	5.44	5.99	5.77	5.53	5.99	1.74	1.82	1.69	1.85	1.82	1.35
12	5.87	6.19	5.93	6.21	5.35	5.4	1.89	1.8	2.33	2.42	1.8	1.94

13	5.96	5.4	5.56	5.21	5.69	6.48	2.52	1.99	2.52	1.88	1.99	1.94
14	5.94	5.6	5.93	5.52	5.53	6.21	2.52	1.96	2	1.92	1.96	1.56
15	5.87	5.44	5.4	5.44	5.51	5.6	1.85	2	1.58	1.94	2	1.9
16	5.77	5.31	6.21	5.81	5.51	6.23	1.83	1.75	1.71	1.92	1.75	2.35
17	6.21	5	5.99	6.21	6.19	5.2	1.85	1.95	1.96	2.08	1.95	2.08
18	6.32	6.21	5.89	6.15	5.4	5.56	1.62	1.65	2.4	1.89	1.65	1.71
19	6.21	5.34	5.78	5.9	5.6	5.4	1.85	1.98	2.44	1.62	1.98	2.04
20	6	5.48	5.56	5.73	5.21	6.21	2.42	1.75	2.48	1.83	1.75	2.35
21	5.81	5.48	5.21	5.21	5.31	6.27	1.88	1.96	2.08	1.96	1.96	1.35
22	6.21	5.52	5.11	5.94	5.69	6.21	1.92	1.98	2.1	1.96	1.98	2.35
23	6.15	5.69	5.23	5.56	6.21	5.23	1.94	1.75	2	2.04	1.75	2.52
24	5.9	5.23	5.2	5.35	6.02	5.4	1.92	1.95	2	2.08	1.95	1.65
25	5.73	5.59	6.1	5.21	5.48	5.56	2.08	2.4	1.35	1.83	2.4	2
26	5.21	5.44	6.4	5.65	5.98	6.21	1.89	1.93	1.35	2.19	1.93	1.69
27	5.94	5.21	5.97	5.27	5.52	5.21	1.62	1.95	1.94	2.29	1.95	2.33
28	5.56	5.4	6.02	6.21	5.69	6.23	1.83	1.9	1.94	1.85	1.9	2.52
29	5.35	5.23	5.73	5.23	5.23	6.21	1.96	1.94	1.56	1.68	1.94	2
30	5.21	5.59	5.87	5.23	5.69	6.21	1.96	1.88	1.9	2.08	1.88	1.58
31	5.65	5.4	5.88	5.21	5.44	6.23	2.04	1.96	2.35	1.92	1.96	1.71
32	6.23	5.03	6.15	5.4	6.21	6.2	2.08	1.96	2.08	2.4	1.96	1.96

33	6.21	5.35	6.12	5.4	5.4	6.02	1.83	1.97	1.71	1.74	1.97	2.4
34	6.23	5.02	6	5.38	5.23	6.3	2.19	1.48	2.04	2.33	1.48	2.44
35	6.11	5.23	5.78	5.21	5.69	6.98	2.29	2.22	2.35	2.52	2.22	2.48
36	6.23	5.53	5.99	5.44	5.4	6.87	1.85	1.95	1.35	2.52	1.95	2.35
37	5.4	5.35	5.4	5.27	5.88	6.15	1.68	1.75	2.35	1.85	1.75	2.08
38	5.4	5.69	6.48	5.31	5.87	6.03	2.08	2.48	2.52	1.83	2.48	1.71
39	6.06	5.53	6.21	5.4	5.49	6.32	1.92	2.21	1.65	1.85	2.21	2.04
40	5.21	5.51	5.6	5.44	5.67	6.02	2.4	2.35	2	1.62	2.35	2.35
41	5.44	5.51	6.23	5.77	5.89	5.32	1.74	2.35	1.69	1.85	2.35	1.35
42	5.27	6.19	5.2	5.42	5.46	5.89	2.33	2.48	2.33	2.42	2.48	2.35
43	5.31	5.4	5.56	5.21	5.69	5.48	2.52	2.17	2.52	1.94	2.17	2.52
44	5.4	5.6	5.4	5.52	5.8	5.88	2.52	2.21	2	1.96	2.21	1.65
45	5.44	5.21	6.21	5.44	6.2	6.11	1.85	2	1.58	1.83	2	2
46	5.77	5.31	6.27	6.22	5.03	5.99	1.83	1.75	1.71	1.98	1.75	1.69
47	6.21	5.69	6.21	6.32	5.19	6	1.85	2.08	1.96	1.99	2.08	2.33
48	5.21	6.21	5.23	6.21	5.4	6.12	1.62	1.65	2.4	1.85	1.65	2.52
49	5.52	6.02	5.4	6.2	5	5.9	1.85	2	2.44	1.68	2	2
50	5.44	5.48	5.56	6.03	5.2	6.2	2.42	1.75	2.48	1.97	1.75	1.58
51	5.81	5.98	6.21	6.012	5.11	6.3	1.88	2.35	2.08	1.92	2.35	1.71
52	6.21	5.52	5.21	5.98	5.59	5.99	1.92	1.98	2.1	2.4	1.98	1.96

53	6.15	5.69	6.23	5.88	5.21	6	1.94	1.75	2	1.74	1.75	2.4
54	5.9	5.23	6.21	6.06	5	5.4	1.92	2.08	2	1.89	2.08	2.44
55	5.73	5.69	6.21	6.03	6.22	6.2	2.08	2.4	1.35	2.52	2.4	2.48
56	5.21	5.44	6.23	5.99	5.4	6.01	1.89	2.21	1.35	2.52	2.21	2.08
57	5.94	6.21	6.2	5.87	5.49	6.15	1.62	2.29	1.94	1.85	2.29	2.1
58	5.56	5.4	6.02	5.96	5.35	6.3	1.83	2.52	1.94	1.83	2.52	2
59	5.35	5.23	6.3	5.94	5.42	5.89	1.96	1.94	1.56	1.85	1.94	2
60	5.21	5.69	6.98	5.87	5.4	6.35	1.96	2.21	1.9	1.62	2.21	1.35
61	5.65	5.4	6.87	5.77	6	5.95	2.04	1.96	2.35	1.85	1.96	1.35
62	5.27	5.88	6.15	6.21	5.11	6.02	2.08	2.25	2.08	2.42	2.25	1.94
63	6.21	5.87	6.03	6.32	5.69	5	1.83	2.04	1.71	1.88	2.04	1.94
64	5.7	5.49	6.32	6.21	5.49	6.01	2.19	1.48	2.04	1.92	1.48	1.56
65	5.23	5.67	6.02	6	5.3	6.22	2.29	1.93	2.35	1.94	1.93	1.9
66	5.76	5.89	5.32	5.81	5.44	5.99	1.85	1.95	1.35	1.92	1.95	2.35
67	5.4	5.46	5.89	5.8	6.19	5.93	1.68	1.75	2.35	2.08	1.75	2.08
68	5.4	5.69	5.48	6.15	5.4	5.56	2.08	2.48	2.52	1.89	2.48	1.71
69	5.38	5.8	5.88	5.9	5.6	5.93	1.92	1.94	1.65	1.62	1.94	2.04
70	5.21	6.2	6.11	5.73	5.88	5.4	2.4	1.97	2	1.9	1.97	2.35
71	5.44	5.03	5.99	5.21	5.31	6.21	1.74	1.98	1.69	1.96	1.98	1.35
72	5.27	5.19	6	5.94	5	5.99	2.33	1.8	2.33	1.96	1.9	2.35

73	5.31	5.4	6.12	5.99	6.21	5.89	2.52	1.96	2.52	2.04	1.96	1.88
74	5.4	5	5.9	5.55	5.34	5.3	2.52	1.99	2	2.08	1.99	1.65
75	5.44	5.2	6.2	5.21	5.48	5.56	1.85	1.96	1.58	1.83	1.96	2
76	5.77	5.11	6.3	5.65	5.48	5.21	1.83	1.94	1.71	2.19	1.94	1.69
77	5.42	5.59	5.99	6.23	5.52	5.11	1.85	1.96	1.96	2.29	1.96	2.33
78	5.21	5.21	6	6.21	5.69	5.23	1.62	1.65	2.4	1.85	1.65	2.52
79	5.52	5	5.4	6.23	5.23	5.2	1.85	2	2.44	1.68	2	2
80	5.44	6.22	6.2	6.11	5.59	6.1	2.42	1.75	2.48	2.08	1.75	1.58

Brainstem Auditory Evoked Potential(BAEP)												
INTERPEAK latency III-V							**INTERPEAK latency I-V**					
Right Ear				**Left Ear**			**Right Ear**			**Left Ear**		
Sl.No	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**
1	2.1	1.54	2.32	2.13	1.58	2	4.15	3.79	4.32	3.99	3.79	3.81
2	2	2.23	2.25	1.78	1.87	2.88	4.33	3.88	3.99	3.23	3.21	3.98
3	2.48	1.75	2.4	1.67	1.77	2.1	4.23	4.5	3.23	3.77	4.75	4.15
4	1.75	1.63	2.34	1.97	2.42	1.97	4.29	3.81	3.77	4.15	3.98	4.15
5	2.32	2.21	1.9	2.11	1.46	2.32	4.99	4.65	4.15	3.5	4.19	4.33
6	2.12	1.88	2.35	1.98	1.67	1.93	4.89	3.82	3.5	3.27	3.21	4.23
7	2.04	2	2.4	1.77	1.85	1.97	4.98	3.86	4.27	3.54	3.33	4.29
8	2.1	1.96	1.99	2.42	1.5	1.83	4.06	4.04	4.54	3.35	3.69	3.99
9	2.13	2.22	2.36	2.4	2.33	1.99	3.88	3.78	4.45	3.81	3.21	3.89
10	2	2.04	1.97	1.86	2.69	2.32	3.86	3.79	4.81	3.98	3.02	3.98
11	2.01	1.77	1.96	1.58	2.67	2.21	3.97	3.21	4.98	4.15	3.03	4.06
12	1.88	2.42	1.8	2.08	1.63	1.97	3.82	4.75	4.15	4.52	3.25	3.88
13	1.94	2.34	2.12	2.04	2.38	2.02	4.15	3.98	4.52	3.79	3.52	3.86

14	2.2	1.99	1.95	2.81	1.6	1.69	3.91	4.19	3.79	3.97	3.69	3.97
15	1.87	1.85	2.35	2.79	1.75	2.22	3.95	3.77	3.97	4.3	3.5	3.82
16	2.42	1.87	2.36	2	1.58	1.95	3.96	3.84	4.3	4.27	4.04	4.15
17	2.4	2.33	2.37	1.92	1.96	2.12	3.85	3.83	4.27	4.23	3.71	4.91
18	1.98	2.69	2.22	1.93	1.92	1.88	3.81	4.21	4.23	3.96	4.21	4.95
19	1.87	2.67	2.31	2	2.69	2.34	3.98	4.02	3.96	4.02	3.88	4.96
20	2.08	1.99	2.22	1.63	2.04	2.08	4.15	4.04	4.02	3.89	3.63	4.85
21	2.04	2.38	2.31	2	1.67	2.17	4.52	4.25	3.89	3.99	4.08	4.81
22	2.81	1.85	1.97	1.97	2.13	1.9	3.79	3.88	3.99	4.15	4.88	4.98
23	2.79	1.75	2.11	1.71	2.22	2	3.97	3.69	4.15	4.33	4.98	4.15
24	2	1.58	1.98	2.21	2.31	1.88	4.21	3.82	4.33	3.96	4.87	4.52
25	1.92	1.96	1.85	2.48	1.75	2.12	4.25	4.04	3.96	3.97	4.97	3.79
26	1.98	1.92	1.88	2	2.24	1.99	3.91	3.71	3.97	3.9	4.98	3.97
27	2	2.69	2.34	2.22	1.29	2.33	3.95	4.21	3.9	4.25	4.99	4.21
28	1.87	2.04	2.08	2.24	1.88	2.32	4.02	3.88	4.25	3.98	4	4.25
29	2	1.99	2.17	2.04	2	2.36	3.73	3.63	3.98	4.06	4.04	3.91
30	2.32	2.13	2.21	1.99	1.96	1.98	3.98	4.08	4.06	3.87	4.96	3.95
31	1.71	2.34	2.3	2.13	2.11	1.99	4.15	3.9	3.87	3.99	4.94	4.02
32	1.98	1.38	2.25	2.33	1.99	1.35	4.33	3.89	3.99	3.98	3.98	3.73
33	2.48	1.75	2.98	2.13	1.77	1.98	3.86	4.23	3.98	4.3	3.76	3.98

34	1.87	1.63	2.35	1.99	2.42	1.1	3.88	3.81	4.3	4.15	3.98	4.15
35	1.99	1.29	2.36	2	2	1.36	3.9	3.87	4.15	4.25	4.19	4.33
36	1.69	1.88	2.88	2.23	2.1	1.95	4.24	4.11	4.25	4.2	4.21	4
37	2.04	2	2.36	2.1	2.31	2.37	3.98	3.76	3.9	4	3.97	3.88
38	1.95	1.96	2.97	2.42	2.43	1.83	4.06	4.04	3.86	4.26	3.89	3.9
39	2.13	1.58	2	2.4	2.33	2.4	4.32	3.75	4.26	3.81	4.21	4.24
40	1.78	1.87	2.88	1.94	2.69	1.89	3.99	3.79	3.81	3.98	4.02	3.98
41	1.67	1.77	2.1	1.99	2.67	2.4	3.23	3.21	3.98	4.15	4.04	4.06
42	1.97	2.42	1.97	2.08	1.63	2.24	3.77	4.75	4.15	4.15	3.79	4.32
43	2.11	1.46	2.32	2.1	1.54	2.32	4.15	3.98	4.15	4.33	3.88	3.99
44	1.98	1.67	1.93	2	2.23	2.25	3.5	4.19	4.33	4.23	4.5	3.23
45	1.77	1.85	1.97	2.48	1.75	2.4	3.27	3.21	4.23	4.29	3.81	3.77
46	2.42	1.5	1.83	1.75	1.63	2.34	3.54	3.33	4.29	4.99	4.65	4.15
47	2.4	2.33	1.99	2.32	2.21	1.9	3.35	3.69	3.99	4.89	3.82	3.5
48	1.86	2.69	2.32	2.12	1.88	2.35	3.81	3.21	3.89	4.98	3.86	4.27
49	1.58	2.67	2.21	2.04	2	2.4	3.98	3.02	3.98	4.06	4.04	4.54
50	2.08	1.63	1.97	2.1	1.96	1.99	4.15	3.03	4.06	3.88	3.78	4.45
51	2.04	2.38	2.02	2.13	2.22	2.36	4.52	3.25	3.88	3.86	3.79	4.81
52	2.81	1.6	1.69	2	2.04	1.97	3.79	3.52	3.86	3.97	3.21	4.98
53	2.79	1.75	2.22	2.01	1.77	1.96	3.97	3.69	3.97	3.82	4.75	4.15

54	2	1.58	1.95	1.88	2.42	1.8	4.3	3.5	3.82	4.15	3.98	4.52
55	1.92	1.96	2.12	1.94	2.34	2.12	4.27	4.04	4.15	3.91	4.19	3.79
56	1.93	1.92	1.88	2.2	1.99	1.95	4.23	3.71	4.91	3.95	3.77	3.97
57	2	2.69	2.34	1.87	1.85	2.35	3.96	4.21	4.95	3.96	3.84	4.3
58	1.63	2.04	2.08	2.42	1.87	2.36	4.02	3.88	4.96	3.85	3.83	4.27
59	2	1.67	2.17	2.4	2.33	2.37	3.89	3.63	4.85	3.81	4.21	4.23
60	1.97	2.13	1.9	1.98	2.69	2.22	3.99	4.08	4.81	3.98	4.02	3.96
61	1.71	2.22	2	1.87	2.67	2.31	4.15	4.88	4.98	4.15	4.04	4.02
62	2.21	2.31	1.88	2.08	1.99	2.22	4.33	4.98	4.15	4.52	4.25	3.89
63	2.48	1.75	2.12	2.04	2.38	2.31	3.96	4.87	4.52	3.79	3.88	3.99
64	2	2.24	1.99	2.81	2	1.97	3.97	4.97	3.79	3.97	3.69	4.15
65	2.22	1.29	2.33	2.79	1.75	2.11	3.9	4.98	3.97	4.21	3.82	4.33
66	2.24	1.88	2.32	2.2	1.58	1.98	4.25	4.99	4.21	4.25	4.04	3.96
67	2.04	2	2.36	1.92	1.96	1.85	3.98	4	4.25	3.91	3.71	3.97
68	1.99	1.96	1.98	1.98	1.92	2	4.06	4.04	3.91	3.95	4.21	3.9
69	2.13	2.11	1.99	2.1	2.69	2.34	3.87	4.96	3.95	4.02	3.88	4.25
70	2.33	1.99	1.35	1.87	2.04	2.08	3.99	4.94	4.02	3.73	3.63	3.98
71	2.13	1.77	1.98	2	1.99	2.17	3.98	3.98	3.73	4	4.08	4.06
72	1.99	2.42	1.1	2.32	2.13	2.21	4.3	3.76	3.98	4.15	3.9	3.87
73	2	2	1.36	1.71	2.34	2.3	4.15	3.98	4.15	4.33	3.89	3.99

74	2.23	2.1	1.95	1.98	1.38	2.25	4.25	4.19	4.33	3.86	3.88	3.98
75	2.1	2.31	2.37	2.48	1.75	2.98	4.2	4.21	4	3.88	3.81	4.3
76	2.42	2.43	1.83	1.87	1.63	2.35	4	3.97	3.88	3.9	3.87	4.15
77	2.4	2.33	2.4	1.99	1.29	2.36	4.26	3.89	3.9	4.24	4.11	4.25
78	1.94	2.69	1.89	1.69	1.88	2.88	3.81	4.21	4.24	3.98	3.76	4.23
79	1.99	2.67	2.4	2.04	2	2.36	3.98	4.02	3.98	4.06	4.04	3.86
80	2.08	1.63	2.24	1.95	1.96	2.97	4.15	4.04	4.06	4.32	3.75	4.26

Brainstem Auditory Evoked Potential(BAEP)													
AMPLITUDE Ratio (V/I)							AMPLITUDE Ratio (V/I)						
Right Ear				Left Ear			Right Ear				Left Ear		
Sl.No	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3	Sl.No	PHASE 1	PHASE 2	PHASE 3	PHASE 1	PHASE 2	PHASE 3
1	0.83	1.12	1.65	0.55	1.39	0.48	41	0.89	0.48	1.43	0.73	1.22	0.46
2	0.72	0.8	0.64	1.01	1.01	0.28	42	0.76	0.28	0.33	0.82	0.8	0.29
3	1.3	0.48	1.3	0.89	1.39	1.22	43	0.59	1.22	0.61	0.83	1.39	0.57
4	1.84	0.28	0.77	0.76	1.22	0.96	44	0.86	0.8	1.68	0.72	1.01	0.48
5	1.22	1.22	1	0.59	1.43	0.55	45	0.75	1.39	1.2	1.3	1.39	1.22
6	1.34	0.8	1.33	0.86	1.39	1.01	46	0.88	1.01	1.23	1.84	1.53	1.3
7	0.22	1.39	1.66	0.75	1.01	0.89	47	1	1.39	1.12	1.22	0.88	0.68
8	0.48	1.01	1.56	0.88	1.39	0.76	48	0.27	1.22	1	1.34	1.03	1.6
9	1.21	1.39	0.46	0.79	0.76	0.59	49	1.12	1.43	0.48	0.22	1.01	1.03
10	1.44	1.53	0.29	0.27	0.27	0.86	50	0.8	1.39	0.28	0.48	0.13	1.38
11	1.4	0.88	0.57	1.12	0.68	0.75	51	0.48	1.01	1.22	1.21	0.48	1.64
12	1.5	1.03	0.48	0.8	0.9	0.88	52	0.99	1.39	0.96	1.44	0.98	0.58
13	0.64	1.01	1.22	0.48	1.53	1	53	1.1	0.76	0.55	1.4	1.29	0.06
14	1.33	0.13	1.3	0.99	0.88	0.27	54	0.59	0.27	1.01	1.5	1.39	1.13
15	1.78	0.48	0.68	1.1	1.03	1.12	55	0.86	0.68	0.89	0.64	0.8	0.21
16	1.34	0.98	1.6	0.59	1.01	0.8	56	0.75	0.9	0.76	1.33	1.1	0.32
17	0.87	1.29	1.03	0.86	1.22	0.48	57	0.88	1.53	0.59	1.78	1.3	0.42
18	0.41	1.39	1.38	0.75	1.23	0.99	58	1.53	0.88	0.86	1.34	1.84	0.67
19	0.52	0.8	1.64	0.88	0.28	1.1	59	0.27	1.03	0.75	0.87	1.22	0.49
20	0.32	1.1	0.58	1.53	1.22	1.3	60	1.12	1.01	0.88	0.41	1.34	0.28

21	1.04	1.3	0.06	0.27	1.22	1.4	61	0.8	1.22	1	0.52	0.22	0.11
22	1.1	1.84	1.13	1.12	1.39	1.22	62	1.23	1.23	0.27	0.32	0.48	0.91
23	1.3	1.22	0.21	0.8	1.01	1.34	63	1.33	0.28	1.12	1.04	1.21	0.87
24	1.18	1.34	0.32	1.23	1.39	0.22	64	0.56	1.22	0.8	1.1	1.44	0.41
25	1.2	0.22	0.42	1.33	1.33	0.48	65	1.1	1.22	0.48	1.3	1.4	0.52
26	1.22	0.48	0.67	0.56	1.66	1.21	66	0.59	1.39	0.99	1.18	1.5	0.32
27	1.43	1.21	0.49	1.1	1.56	1.44	67	0.86	1.01	1.1	1.2	0.64	1.04
28	0.33	1.44	0.28	0.59	1.22	1.4	68	0.75	1.39	1.3	1.22	1.33	1.1
29	0.61	1.4	0.11	0.86	0.29	1.5	69	0.88	1.33	1.84	1.43	0.59	1.3
30	1.68	1.5	0.91	0.75	0.57	0.5	70	1.53	1.66	1.22	0.33	0.86	1.18
31	1.2	0.64	0.87	0.88	1.53	0.67	71	0.27	1.56	1.34	0.61	0.75	1.2
32	1.23	1.33	0.41	1.53	0.27	0.62	72	1.12	1.22	0.22	1.68	0.88	1.22
33	1.12	0.59	0.52	0.27	1.12	1.65	73	0.8	0.29	0.48	1.2	0.76	1.43
34	1	0.86	0.32	1.12	0.8	0.64	74	0.48	0.57	1.21	1.23	0.27	1
35	0.48	0.75	1.04	0.8	1.23	1.3	75	0.28	1.53	1.44	1.12	1.12	0.61
36	0.28	0.88	1.1	0.48	1.33	0.77	76	1.22	0.27	1.4	1	1.2	1.68
37	1.22	0.76	1.3	0.28	1.12	1	77	0.5	1.12	1.5	0.88	1	1.2
38	0.96	0.27	1.18	1.22	0.8	1.33	78	1	0.8	0.5	0.28	0.28	1.23
39	0.55	1.12	1.2	0.5	0.48	1.66	79	0.73	1.23	0.67	1.22	1.22	1.12
40	1.01	0.8	1.22	1	0.28	1.56	80	0.82	1.33	0.62	0.96	0.8	1

Visual Evoked Potential(VEP)												
WAVE P100 latency							**WAVE P100 Amplitude**					
Right Eye				**Left Eye**			**Right Eye**			**Left Eye**		
Sl.No	**PHASE 1**	**PHASE-2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**	**PHASE 1**	**PHASE 2**	**PHASE 3**
1	96.92	95.96	99.5	96.96	93.4	99.54	7.9	8.77	8.7	7.87	6.81	6.77
2	97.11	96.88	98	97	93.22	98.45	8.92	6.76	7	7.66	6.66	8.18
3	96.94	97	98	97.23	93	99	7.67	8.87	7.68	7.82	8.66	6.88
4	96.87	97.23	97.7	97.11	93.85	99.5	8.77	7.83	7.87	8	8.78	8.06
5	96.76	97	98.65	96.84	95.23	98	7	7.78	7.62	7.83	8.87	7.78
6	97.3	93.78	98.53	96.88	97	98.23	6.86	8.16	7.7	7.29	8.76	6.87
7	96.96	93.7	97.24	97.12	97.05	98	6.98	8.88	7.78	8.16	8.78	8.27
8	97	94.2	98.32	96.97	93.56	99.53	7.77	8.78	7.88	7.89	8.96	7.11
9	96.89	98	98	96.87	95.89	96.54	7.66	8.81	6.77	7.27	9.86	7.7
10	96.87	97	99.87	97	95.88	98.56	8.5	8.88	7	7.91	7.66	8.77
11	96.96	95.23	99.56	97.23	94.94	99	7.78	8.78	7.6	7.86	8.69	8.8
12	96.78	97.43	99.8	97	94.89	96.32	8.76	7.37	8.06	7.84	6.31	6.18
13	97.21	95.21	99.87	96.23	95.5	100.56	8.4	8.31	7	6.71	7.6	7.77

14	96.76	93	98.3	96.47	94.2	96	8.32	8.38	6.87	8.92	8.88	6.66
15	97.29	97	98	96.75	94.87	100.87	7.66	8.88	8.27	7.79	8.8	8.87
16	97	93	98.45	96.88	94.76	96.34	8.73	8.76	7.11	7.9	7.83	8.78
17	96.99	93.7	99	96.87	93.6	97.68	7.9	6.86	7.7	7.88	7.88	7
18	96.98	95	98.5	97.23	93.93	97.45	6.78	6.87	8.77	6.86	8.71	6.01
19	97.21	96.88	98.88	96.43	93.11	97.4	7.33	7.83	8.8	7.86	7.83	6.7
20	96.8	93.12	99	97.21	95.89	96	7.77	6	6.18	6.73	7.9	6.87
21	97.32	97.9	97	97	94.87	97.88	7.86	6.63	7.77	7.79	8.39	8.78
22	96.9	93.1	97.23	96.89	94.2	97.33	8	6.68	6.66	8	8.33	8.2
23	96.87	93.7	97.89	96.59	95.78	97	7.83	6.87	8.87	7.78	8	8
24	96.99	93.22	97.87	96.76	95.32	96	7.29	6.88	8.78	8.77	8.88	8.77
25	97.07	93.21	99.88	96.88	95.76	97.9	8.16	6.37	8	7.7	8.5	7.77
26	96.65	95.11	99.43	96	95.32	97.43	7.89	6.86	6.01	8	8.88	8.88
27	97.21	97.12	99.56	97.12	95	98.88	7.27	8.66	6.7	8.1	6.98	8.62
28	96.88	97.4	99.99	96.76	96	96.43	7.91	7.8	6.87	7.84	8.16	8.8
29	97.03	96.23	99	96.73	96.38	96.22	7.23	7.77	6.71	7.9	6.66	8.6
30	97	93.4	99.54	96.96	94.22	96.12	7.21	8.66	7.1	9	8.88	7.88
31	96.96	93.22	98.45	96.75	94.8	96	7.96	8.66	8.8	8.89	8.91	7.78
32	97.21	93	99	96.56	94.6	96.23	8.92	6.76	8	8.77	8.88	8.76
33	97.2	93.85	99.5	97.11	94.67	96.22	6.8	8.66	7	9.63	8.88	8.77

34	96.96	95.23	98	96.87	96.87	96.21	7.87	7.83	7.87	8.2	8.88	7.86
35	96.99	97	98.23	96.76	96	97.89	6.93	7.78	7.62	7.83	8.97	7
36	96.88	97.05	98	97.23	94	97	6.86	8.16	7.7	7.29	6	7.77
37	95.99	93.56	99.53	97.4	96.65	97.97	7.9	6.88	8.26	8.16	7.66	8.27
38	96.84	95.89	96.54	97.22	97.1	96.88	6.73	6.76	7.88	7.88	6.93	7.11
39	96.88	95.88	98.56	96.96	93.22	98.54	7.87	6.81	6.77	7.27	6.86	7.7
40	96.87	94.94	99	96.87	93.78	98.39	7.66	6.66	8.18	7.91	7.83	7.77
41	96.95	94.89	96.32	97.23	93.32	97.22	7.82	8.66	6.88	7.88	6.63	8.8
42	96.87	97.88	100.56	97.33	95.95	98.8	8	8.78	8.06	7.67	6.31	7
43	95.98	94.2	96	97.3	95	98.46	7.83	8.87	7.78	7.9	8.77	8.7
44	95.95	94.87	100.87	97.32	97.1	98.32	7.29	8.76	6.87	8.92	6.76	7
45	97.11	94.76	96.34	96.89	95.95	98.68	8.16	8.78	8.27	7.67	8.87	7.68
46	97.02	93	97.68	96.88	95	98.56	7.89	8.96	7.11	8.77	7.83	7.87
47	96.47	93.93	97.45	96.96	95	98	7.27	9.86	7.7	7	7.78	7.62
48	96.75	93.11	97.4	96	96.11	98.56	7.91	7.66	8.77	6.86	8.16	7.7
49	96.88	95.89	96	96.22	96.7	97	7.86	8.69	8.8	6.98	8.88	7.78
50	96.87	94.87	97.88	96.2	96	99.54	7.84	6.31	6.18	7.77	8.78	7.88
51	97.21	94.2	97.33	96.87	95.12	98.54	6.71	7.6	7.77	7.66	8.81	6.77
52	96.43	95.78	97	96.76	95.96	99.5	8.92	8.88	6.66	8.5	8.88	7
53	97	95.32	96	97	96.88	98	7.79	8.8	8.87	7.78	8.78	7.6

54	97	95.76	97.9	96.96	97	98	7.9	7.83	8.78	8.76	7.37	8.06
55	96.89	95.32	97.43	97.11	97.23	97.7	7.88	7.88	7	8.4	8.31	7
56	97.22	95	98.88	96.89	97	98.65	6.86	8.71	6.01	8.32	8.38	6.87
57	96.76	96	96.43	96.87	93.78	98.53	7.86	7.83	6.7	7.66	8.88	8.27
58	96.88	96.38	96.22	96.96	93.7	97.24	6.73	7.9	6.87	8.73	8.76	7.11
59	97.16	94.22	96.12	96.78	94.2	98.32	7.79	8.39	8.78	7.9	6.86	7.7
60	97.14	94.8	96	97.32	98	98	8	8.33	8.2	6.78	6.87	8.77
61	96.76	94.6	96.23	96.76	97	99.87	7.78	8	8	7.33	7.83	8.8
62	97.1	94.67	96.22	97.32	95.23	99.56	8.77	8.88	8.77	7.77	6	6.18
63	96.96	96.87	96.21	97.22	97.43	99.8	7.7	8.5	7.77	7.86	6.63	7.77
64	96.75	96	97.89	97	94	99.87	8	8.88	8.88	8	6.68	6.66
65	97.21	96.5	97	96.38	93	98.3	8.1	6.98	8.62	7.83	6.87	8.87
66	96.87	96.65	97.97	97.22	97	98	7.84	8.16	8.8	7.29	6.88	8.78
67	96.87	97.1	96.88	96.8	93	98.45	7.9	6.66	8.6	8.16	6.37	8
68	96.76	93.22	98.54	96.38	93.7	99	9	8.88	7.88	7.89	6.86	6.01
69	96.97	93.78	98.39	96.67	95	98.5	7.87	8.91	7.78	7.27	8.66	6.7
70	97	93.32	97.22	96.87	96.88	98.88	8.77	8.88	8.76	7.91	7.8	7.2
71	96.57	95.95	98.8	96.67	93.12	99	9.63	8.88	8.77	7.23	7.77	6.71
72	96.96	95	98.46	96.5	97.9	97	8.2	8.88	7.86	7.21	8.66	7.1
73	96.87	97.1	98.32	96.65	93.1	97.23	7.83	8.97	7	7.96	8.66	8.8

74	97.21	95.95	98.68	97.21	93.7	97.89	7.29	6	7.77	7.9	6.76	8
75	95.98	95	98.56	96.88	93.22	97.87	8.16	7.66	8.27	6.8	8.66	7
76	97.2	95	98	97	93.21	98	7.88	6.93	7.11	7.87	7.83	7.87
77	96.93	96.11	98.56	97.99	95.11	97	7.27	6.86	7.7	7	7.78	7.62
78	96.89	96.7	97	96.96	97.12	99.56	7.91	7.83	7.77	6.86	8.16	7.7
79	96.88	96	99.54	97.21	97.4	99.99	7.88	6.63	8.8	7.9	7	8.26
80	96.96	95.12	98.54	97.88	96.23	99	7.67	6.31	7	6.73	6.76	7.88